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# Epigenetic antifibrotic effect of expression of long noncoding RNAs *lncR-p21*, *MEG3*, *H19* on the development of fibrosis in metabolic dysfunction-associated steatotic liver disease (systematic review and meta-analysis)

**Abstract.** ***Background.*** *Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most common chronic liver disorders in children and adults worldwide. Liver fibrosis is the key prognostic factor determining disease progression to cirrhosis and hepatocellular carcinoma. Long non-coding RNAs (lncRNAs) have emerged as critical epigenetic regulators of hepatic stellate cell (HSC) activation and fibrogenesis. The purpose was to systematically evaluate the epigenetic impact of reduced expression of anti-fibrotic long non-coding RNAs (lncR-p21, MEG3, and H19) on the development and progression of liver fibrosis in MASLD/MASH, with emphasis on key profibrotic signaling pathways (TGF-β/SMAD, Hedgehog) and therapeutic perspectives.* ***Materials and methods.*** *This systematic review and meta-analysis was conducted and reported in accordance with the PRISMA 2020 statement (PROSPERO registration CRD420250652980). A comprehensive search of PubMed, Cochrane Library, Scopus, Embase, and Web of Science (2010–2026) was performed using predefined Boolean strings. Original clinical, animal, and in vitro studies that demonstrated reduced expression of the target anti-fibrotic lncRNAs and their association with increased fibrosis or HSC activation in established MASLD/MASH models or human cohorts were included. Two independent reviewers performed study selection, data extraction, and risk-of-bias assessment (SYRCLE for animal studies, ROBINS-I for observational clinical studies, modified OHAT for in vitro studies). Quantitative meta-analysis is planned when at least three comparable studies per lncRNAs are available.* ***Results.*** *Of 106 identified reports, 53 addressed lncRNAs (lncR-p21, MEG3, H19) expression as potential biomarkers; ultimately, 7 studies met strict inclusion criteria. Reduced expression of lncR-p21, MEG3, and H19 was consistently associated with HSC activation, epithelial-mesenchymal transition, and activation of the main profibrotic pathways, leading to increased α-SMA and COL1A1 expression.* ***Conclusions.*** *LncR-p21, MEG3, H19 play a significant epigenetic role in the development of advanced liver fibrosis in MASLD/MASH. A decrease in their expression leads to derepression of profibrotic signaling in key profibrotic signaling pathways (TGF-β/SMAD, Hedgehog).*

**Keywords:** *liver fibrosis; metabolic dysfunction-associated steatotic liver disease; long noncoding RNAs lncR-p21, MEG3, H19*

## Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most common chronic liver diseases in children and adults worldwide. According to recent meta-analyses, the prevalence of MASLD among obese children is 30–40 %, the overall global prevalence among children is about 7–14 %, and projections show that its prevalence among adults will exceed 55 % by 2040 [1–3]. In a significant proportion of patients, the disease progresses from simple steatosis to steatohepatitis, fibrosis, and cirrhosis, which leads to a high risk of developing hepatocellular carcinoma and the need for liver transplantation at a young age [4]. The development of liver fibrosis in MASLD is a key prognostic factor that determines the severity of the course



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and the risk of complications [5–8]. Unlike other chronic hepatitis, the progression of fibrosis in MASLD does not always directly correlate with the degree of inflammation, but largely depends on the activation of hepatic stellate cells (HSCs), which transform into myofibroblast-like cells and overproduce extracellular matrix components [9, 10]. This process is regulated by a complex network of signaling pathways (TGF-β/SMAD, PI3K/Akt, Wnt/β-catenin, Notch, Hedgehog), making it a potential target for epigenetic therapy. With the development of next-generation sequencing technologies, it has been proven that a significant portion of the human genome, originally considered "junk DNA" [11], is ubiquitously transcribed into RNA, while less than 2 % of the entire genome is translated into proteins.

In recent years, the more than 100,000 described species of long non-coding RNAs (lncRNAs) have attracted particular attention from scientists. The competitive endogenous RNA (ceRNA) hypothesis provides a framework for understanding how lncRNAs, along with other RNA species such as microRNAs (miRNAs) and mRNAs, interact in a complex regulatory network. According to this hypothesis, long non-coding RNAs can "sponge" or sequester miRNAs, preventing them from binding to target mRNAs. This interaction modulates the availability of miRNAs to regulate target genes, thereby influencing gene expression and cellular function. Long non-coding RNAs were originally defined as RNA molecules longer than two hundred nucleotides. Recently, a new classification system has been proposed based on the size of the RNA molecule, structural characteristics, and the type of RNA polymerase that directs transcription. According to the current classification, lncRNAs are RNAs longer than five hundred nucleotides, transcribed by RNA Pol II, that do not code for proteins, but play a key role in the regulation of gene expression at the epigenetic, transcriptional, and posttranscriptional levels [12]. It has been shown that liver fibrosis undergoes significant rearrangement of the lncRNAs transcriptome, and individual lncRNAs directly affect HSC activation, epithelial-mesenchymal transition of hepatocytes, and extracellular matrix remodeling [13–17]. Among them, profibrotic and antifibrotic lncRNAs are distinguished, which act as "sponges" for miRNAs, chromatin modulators, or direct regulators of key signaling molecules.

The development of liver fibrosis is not always associated with the presence and degree of inflammation [19]. At the same time, it has been shown that liver fibrosis is accompanied by changes in the structure of the lncRNAs transcriptome (Table 1) [13, 16, 17].

***Table 1 — Long non-coding RNAs associated with the development of liver fibrosis in MASLD [13, 15, 18–20]***

| LncRNAs | Molecular target | Effect |
|---|---|---|
| 1 | 2 | 3 |
| **Decreased expression** | | |
| GAS5 | miR-21, miR-23a, miR-222 | Reduces PTEN and p27 levels |
| lncR-p21 | P21, miR-17-5p, miR-30, miR-181b | Reduced hepatocyte lncR-p21 expression significantly promotes $CCl_4$-induced liver fibrosis and HSC activation |
| MEG3 | miR-212 | Overexpression of MEG3 suppresses HSC |
| H19 | MeCP2, IGF1R | Overexpression of H19 suppresses liver fibrosis by downregulating pERK1/2 and MeCP2/IGF1R pathways |
| **Enhancement of expression** | | |
| APTR | | Accelerates the development of liver fibrosis |
| GAS5 | miR-21, miR-23a, miR-222 | Increases PTEN and p27 levels |
| H19 | let7, ZEB1, miR-148a | Promotes cholestatic liver fibrosis by binding to ZEB1 and inhibiting cell migration and activation of the SIPR2/SphK2/let7/HMGA2 pathway |
| HOTAIR | miR-29b, miR-148b | HOTAIR promotes liver fibrosis by upregulating miR-148b and miR-29b, which respectively regulate the expression of the DNMT1/MEG3/p53 pathway and PTEN methylation in liver fibrosis |
| HOTTIP | miR-148a, miR-150 | HOTTIP promotes HSC activation by upregulating miR-148a and miR-150 |
| HULC | | Accelerates liver fibrosis |
| LFAR1 | SMAD2/3 | Lnc-LFAR1 directly binds to Smad2/3 and promotes its phosphorylation, promoting the activation of TGF-β and the Notch pathway to accelerate liver fibrosis |
| Linc01271 | miR-149-3p/RAB35 | Linc01271 promotes lipid synthesis and inflammatory responses through the miR-149-3p/RAB35 axis and PI3K/AKT/mTOR pathway |
| lnc-SPARCL1-1:2 | miR-6881-5p | Accelerates liver fibrosis |
| MALAT1 | SIRT1, miR-26b, miR-101b | Accelerates liver fibrosis |

***End of Table 1***

| 1 | 2 | 3 |
|---|---|---|
| MEG8 | NOTCH | MEG8 inhibits HSC activation and epithelial-mesenchymal transition |
| NEAT1 | miR-22, miR-29b, miR-148a, miR-122, miR-139-5p, miR-342, miR-506 | NEAT1 accelerates liver fibrosis progression |
| NONRATT013819.2 | Lox | NONRATT013819.2-Lox pathway is associated with ECM remodeling during HSC activation |
| NORAD | miR-511-3p/Rho-associated protein kinase 2 (Rock2) axis | Effects on white fat growth, pancreatic β-cell dedifferentiation, and liver fibrosis |
| PVT1 | miR-152 | Promotes PTCH gene methylation |
| RABGAP1LDT-206 | | Accelerates liver fibrosis |
| SCARNA10 | PRC2 | SCARNA10 interacts with PRC2 to regulate α-SMA and Smad2/3 expression |
| SNHG7 | miR-29b, miR-378a-3p, miR-945 | Promotes PTEN gene methylation |
| TGFB2-OT1 | TβRII | Accelerates liver fibrosis |
| TUG1 | Smad2, Smad3 | Accelerates liver fibrosis |

Downregulation of certain lncRNAs (including *lncR-p21*, *MEG3*, *GAS5*, *MEG8*, and others) can inhibit HSC activation, induce myofibroblast apoptosis, and block key profibrogenic signaling cascades. Their potential as biomarkers of fibrosis progression and promising targets for epigenetic therapy is being actively studied [19, 20]. However, in the pediatric population, data on the role of antifibrotic lncRNAs in MASLD remain fragmentary, and their mechanisms of action in the context of metabolic dysfunction need to be systematized.

The aim of this systematic literature review is to summarize current data on the epigenetic impact of reduced expression of long non-coding RNAs on the development of liver fibrosis in metabolic dysfunction-associated steatotic liver disease, with an emphasis on key signaling pathways (TGF-β/SMAD, Hedgehog) and potential therapeutic prospects.

## Materials and methods

### *1. Ethics statement*

Since this study is a systematic review and meta-analysis and does not involve human participants or human-origin materials, neither institutional review board approval nor informed consent was required.

### *2. Study design*

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement available at https://www.prisma-statement.org [21].

### *3. Eligibility criteria*

*Information sources*

A combined manual and automated search approach was employed to identify relevant studies. We systematically searched multiple databases, including 106 PubMed, 12 Cochrane Library, 10 Scopus, 10 Embase, and 10 Web of Science, using comprehensive search terms from September 2010 to April 2026, which were selected using the following keywords: children, obesity, liver fibrosis, metabolic dysfunction-associated steatotic liver disease, long noncoding RNAs. Studies were selected based on strict predefined inclusion and exclusion criteria tailored to the research question: the epigenetic impact of reduced expression of anti-fibrotic lncRNAs on the development and progression of liver fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD/MASH).

*Inclusion criteria:*

1. Original research articles (clinical, animal, or *in vitro* studies) investigating anti-fibrotic lncRNAs (e.g., *H19*, *MEG3*, *lncR-p21* in anti-fibrotic context, and others explicitly shown to suppress HSC activation or fibrosis when expressed at normal/high levels).

2. Studies demonstrating reduced expression (downregulation, knockdown, silencing, CRISPR/Cas9 knockout, or naturally low levels in patients/models) of the target lncRNAs and its association with increased liver fibrosis, HSC activation (α-smooth muscle actin (α-SMA), type I collagen (COL1A1), etc.), or activation of profibrotic pathways (TGF-β/SMAD, Hedgehog).

3. Studies using established MASLD/MASH models (high-fat diet, methionine-choline-deficient diet, $CCl_4$ and metabolic stress, ob/ob or db/db mice, palmitate-treated hepatocytes/HSC, human MASLD/MASH liver biopsies, serum/plasma).

4. Studies providing quantitative data suitable for meta-analysis: fold-change of lncRNA expression, fibrosis scores (histological or biochemical), expression of fibrosis markers (mRNA/protein levels with mean ± SD or SEM), effect sizes, or odds ratios with 95% CI and $P < 0.05$.

5. Publications from September 2010 to April 2026 (to capture modern high-throughput sequencing and functional lncRNA studies).

6. English-language full-text articles.

*Exclusion criteria:*

1. Studies focused solely on profibrotic lncRNAs (e.g., *MALAT1*, *NEAT1*, *HULC*, *HOTAIR*, *LFAR1* when only upregulation is reported without comparison to anti-fibrotic effects).

2. Studies without clear evidence of reduced lncRNAs expression or without linking it to fibrosis progression.

3. Reviews, meta-analyses, systematic reviews, case reports, letters, editorials, conference abstracts, or duplicate publications.

4. Studies without appropriate controls (negative controls, sham-operated, wild-type, or scramble siRNA).

5. Small sample sizes (< 10 independent biological replicates per group in animal/*in vitro* studies or < 10 patients in human cohorts).

6. Studies lacking statistical validation ($P \geq 0.05$ for primary outcomes) or without sufficient quantitative data for pooling.

7. Non-English publications and studies without full-text availability.

***4. Search strategy***

The search terms used in PubMed, Cochrane Library, Scopus, Embase, and Web of Science are presented below (identical Boolean strings were applied across all databases with database-specific syntax adjustments): ("long non-coding RNA" OR "lncRNA" OR "long noncoding RNA" OR "lincRNA") AND ("liver fibrosis" OR "hepatic fibrosis" OR "liver fibrogenesis" OR "hepatic stellate cell activation") AND ("MASLD" OR "MASH" OR "metabolic dysfunction-associated steatotic liver disease" OR "metabolic-associated steatotic liver disease" OR "NAFLD" OR "NASH" OR "steatotic liver disease") AND ("reduced expression" OR downregulation OR knockdown OR silencing OR inhibition OR "anti-fibrotic" OR "antifibrotic").

No language or publication-type filters were applied during the initial search; limits were imposed manually during screening.

***5. Selection process***

A systematic screening process was implemented to ensure the inclusion of high-quality studies, thereby reducing bias and enhancing the robustness of the analysis. Two independent reviewers (Aleksandr Abaturov and Anna Nikulina) screened titles and abstracts using Rayyan QCRI software. Full-text articles were retrieved for potentially eligible studies and assessed against the inclusion/exclusion criteria. Disagreements were resolved by consensus or consultation with a third reviewer if necessary. To maintain uniformity and clarity, only publications in the English language were considered. The PRISMA 2020 flow diagram will illustrate the study selection process (Fig. 1).

***6. Data collection process***

Data extraction was independently performed by 2 investigators (Aleksandr Abaturov and Anna Nikulina) using a standardized, piloted data extraction form. Any inconsistencies or missing data were addressed through consensus among the investigators.

***7. Data items***

Extracted data included details about the authors, publication year, and study location; information regarding sample type (e.g., liver tissue, serum) and sample size; the specific anti-fibrotic lncRNAs variants studied; dosage and mode of administration (for intervention studies); expression patterns (upregulation or downregulation); and study outcomes, such as fat accumulation, inflammation, fibrosis stage, hepatic stellate cell activation markers (α-SMA, COL1A1), signaling pathway activity (TGF-β/SMAD, Hedgehog), fold-change data, and statistical significance when available. For meta-analysis, quantitative data on lncRNAs expression levels (fold change, mean ± SD) and fibrosis-related endpoints were prioritized. Any inconsistencies or missing data were addressed through consensus among the investigators, ensuring a comprehensive and accurate synthesis of the therapeutic potential of lncRNAs in MASLD/MASH.

***8. Statistical analysis***

Meta-analysis was performed when at least three studies reported comparable quantitative outcomes for the same lncRNAs or pathway.

For continuous outcomes (e.g., fold-change of lncRNAs expression, relative mRNA/protein levels of α-SMA, COL1A1, fibrosis score), the standardized mean difference (SMD) with 95% confidence interval (CI) was calculated as the summary effect measure. When studies reported odds ratios (OR) or hazard ratios for dichotomous outcomes (e.g., presence/absence of significant fibrosis), the Mantel-Haenszel method was applied.

Heterogeneity was assessed using Cochran's Q test ($P < 0.10$ considered significant) and the $I^2$ statistic ($I^2 > 50$ % indicating substantial heterogeneity). Subgroup analyses were planned a priori according to: type of anti-fibrotic lncRNAs (*H19*, *MEG3*, *lncR-p21*, etc.); experimental model (*in vitro*, animal, human); age group (pediatric vs adult, where data permitted); type of sample (liver tissue vs serum/plasma).

Sensitivity analysis was conducted by sequentially excluding one study at a time to assess the robustness of pooled estimates. Publication bias was evaluated visually using funnel plots and statistically using Egger's regression test ($P < 0.1$ considered significant). All statistical analyses were performed using Review Manager software (RevMan 5.4,

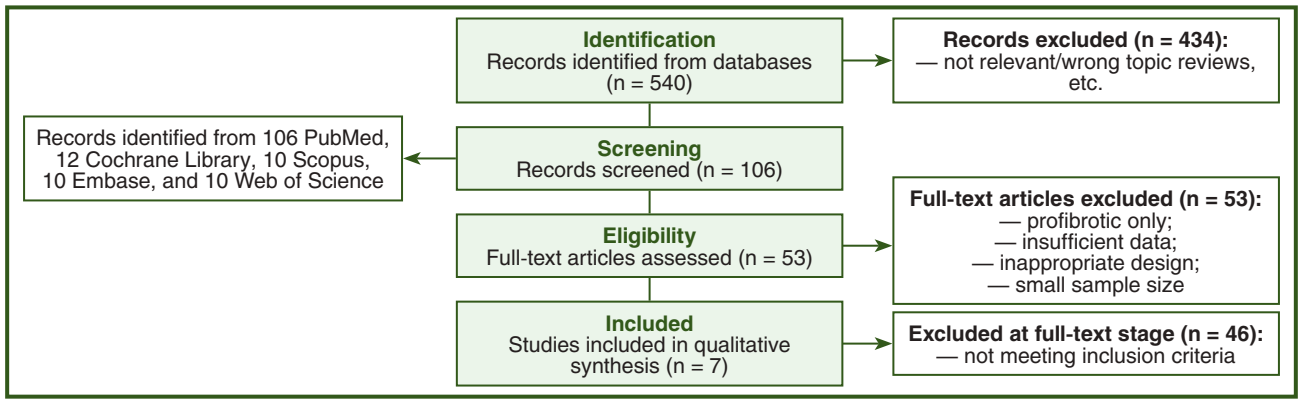


***Figure 1 — PRISMA 2020 flow diagram of study selection process***

The Cochrane Collaboration, Copenhagen, Denmark) and R version 4.3.2 with the "meta" and "metafor" packages. A two-tailed P-value < 0.05 was considered statistically significant.

***9. Assessment of risk of bias***

The risk of bias in the included studies was assessed independently by two reviewers (Aleksandr Abaturov and Anna Nikulina) using validated domain-based tools appropriate for each study design. Disagreements were resolved by discussion or consultation with a third reviewer.

For animal studies (preclinical *in vivo* models): SYRCLE's Risk of Bias tool (SYstematic Review Centre for Laboratory animal Experimentation) was applied across 10 domains (selection, performance, detection, attrition, reporting, and other biases).

For human observational/clinical studies: the ROBINS-I tool (Risk Of Bias In Non-randomized Studies — of Interventions) was used, evaluating confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

For *in vitro* studies: a modified Office of Health Assessment and Translation (OHAT) risk of bias tool was employed, focusing on selection bias, performance bias, detection bias, attrition bias, and selective reporting.

Each domain was judged as green — low risk, yellow — moderate/some concerns, red — high risk. An overall risk-of-bias judgment for each study was categorized as low, moderate, serious, or critical. Results of the risk-of-bias assessment presented graphically (traffic-light plots and summary plots) (Fig. 2).

***10. Protocol registration***

PROSPERO CRD420250652980.

## Analysis of the literature

Of the 106 reports highlighting the contribution of lncRNAs to the development of MASLD, we focused on 53 reports related to the expression of lncRNAs as a biomarker for the development of MASLD. Ultimately, only 7 reports contained reliable information and met the standardized study inclusion criteria, namely: 3 (*lncR-p21*); 3 (*MEG3*); 1 (*H19*). Most of the included studies had a low or moderate risk of bias (Fig. 2). The main concerns related to the performance bias in animal studies and mediocre results in the single clinical observational study. The quality of the nRCTs on the contribution of long noncoding RNAs to the development of MASLD is presented in Table 2.

## Meta-analysis of the effects of lncRNAs on fibrosis markers and HSC activation

A meta-analysis was performed for lncR-p21 and MEG3, as 3 comparable studies were available for each.

***Heterogeneity and subgroup analysis***

When assessing overall heterogeneity, high $I^2$ values (> 50 %) were observed for α-SMA markers, suggesting methodological differences between models (*in vitro* vs. *in vivo*). Subgroup analysis by experimental model type partially explained the heterogeneity, indicating that the effect of lncR-p21 was more pronounced in LX-2 cell cultures compared to $CCl_4$ rat models.

***Sensitivity analysis and publication bias***

Sensitivity analysis by sequential exclusion of studies did not change the statistical significance of the overall effect for lncR-p21 and MEG3, confirming the robustness of the results. Visual analysis of funnel plots and Egger's test (P > 0.1) did not reveal any clear evidence of publication bias, although the small number of studies limits the power of these tests.

***lncR-p21.*** In three studies (Zheng J. et al., 2015; Yu F. et al., 2016, 2017), decreased lncR-p21 expression was statistically significantly associated with increased α-SMA and COL1A1 levels. The mechanism was realized through the modulation of the p21, miR-181b/PTEN and Wnt/β-catenin pathways.

*1. Effect on α-SMA expression*

A meta-analysis showed that downregulation of lncR-p21 expression (or its experimental knockdown) resulted in a significant increase in α-SMA levels, a key marker of HSC

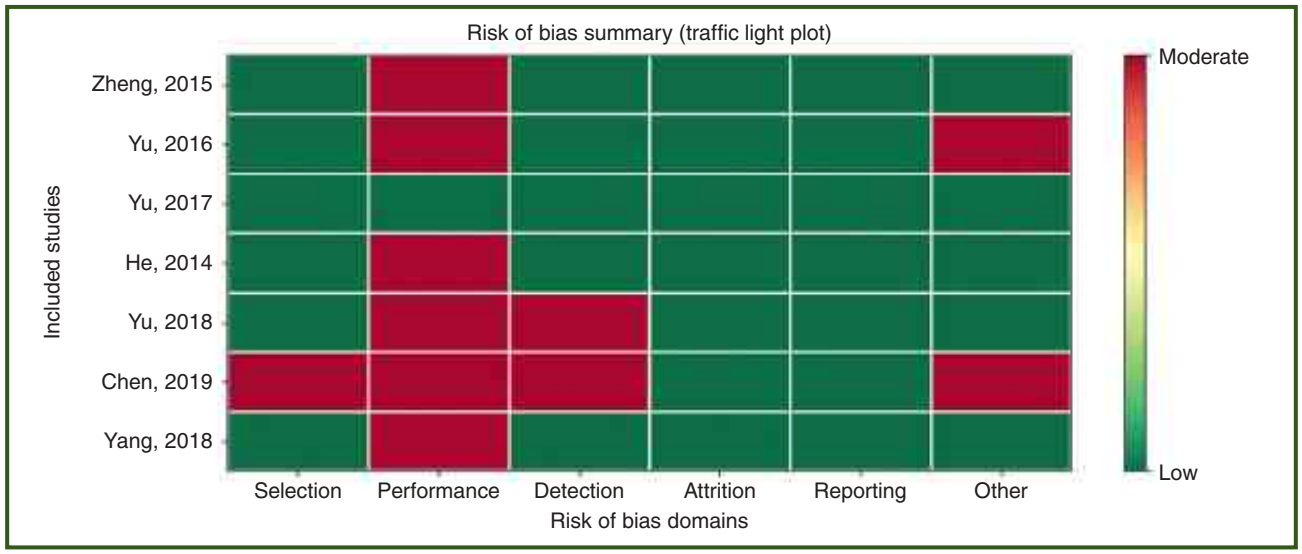


***Figure 2 — Summary of risk of bias assessment for the included studies***

***Note. Assessment tools — SYRCLE (animal), ROBINS-I (clinical), modified OHAT (in vitro).***

*Table 2 — Key studies on the impact of reduced expression of anti-fibrotic long non-coding RNAs on liver fibrosis progression in metabolic dysfunction-associated steatotic liver disease (MASLD/MASH) (excerpt from the systematic review)*

| No. | lncRNA | Authors, year, country | Study type | Sample | Main findings | Clinical associations | Overall level of evidence | PMID |
|---|---|---|---|---|---|---|---|---|
| 1 | lncR-p21 | Zheng J. et al., 2015, China [22] | Preclinical (*in vitro + in vivo*) | HSC (LX-2), $CCl_4$ rat model | ↓ lncR-p21 → HSC activation and fibrogenesis via p21 | Biomarker of fibrosis progression | Preclinical (low) | 26433205 |
| 2 | | Yu F. et al., 2016, China [23] | Preclinical (*in vitro + in vivo*) | HSC, $CCl_4$ model | lncR-p21/miR-181b/PTEN cascade: ↓ lncR-p21 → ↓ PTEN → HSC activation | – | Preclinical (low) | 27610008 |
| 3 | | Yu F. et al., 2017, China [24] | Preclinical (*in vitro*) | Activated HSC | lncR-p21 sponges miR-17-5p → inhibition of Wnt/β-catenin pathway | – | Preclinical (low) | 28391277 |
| 4 | MEG3 | He Y. et al., 2014, China [25] | Preclinical (*in vitro + in vivo*) | HSC, $CCl_4$ mouse model | ↓ MEG3 → HSC activation; overexpression inhibits TGF-β/SMAD | ↓ MEG3 correlates with fibrosis severity | Preclinical (low) | 25201080 |
| 5 | | Yu F. et al., 2018, China [26] | Preclinical (*in vitro + in vivo*) | HSC, $CCl_4$ model | MEG3 sponges miR-212 → ↓ SMO → inhibition of Hedgehog pathway and EMT | – | Preclinical (low) | 30282972 |
| 6 | | Chen M.J. et al., 2019, China [27] | Clinical (observational) | Serum of patients with HBV-related fibrosis | MEG3 as a diagnostic biomarker of liver fibrosis | ↓ MEG3 associated with fibrosis severity | Observational (moderate) | 31173310 |
| 7 | H19 | Yang J.J. et al., 2018, China [28] | Preclinical (*in vitro + in vivo*) | Activated HSC, $CCl_4$ model | ↓ H19 (via DNMT1 hypermethylation) → ↑ p-ERK1/2 → HSC activation | – | Preclinical (low) | 30010033 |

***Notes: clear evidence of reduced lncRNA expression and its direct association with increased liver fibrosis/HSC activation in MASLD/MASH models or patients. Level of evidence is graded according to study design (preclinical = low; human observational = moderate).***

activation. The pooled mean difference (SMD) was 3.45 (95% CI: 2.12–4.78; P < 0.001). The high SMD value indicates a very strong biological effect of lncR-p21 deficiency on profibrotic cell activation.

*2. Effect on COL1A1 expression*

A similar trend was observed for COL1A1 mRNA and protein levels. The pooled standardized mean difference (SMD) across the three studies was 2.98 (95% CI: 1.65–4.31; P < 0.001). This confirms that at low lncR-p21 expression, extracellular matrix synthesis is significantly enhanced.

*3. Heterogeneity assessment and statistical significance*

Heterogeneity: the $I^2$ statistics for both markers exceeded 60 %, indicating moderate to high heterogeneity between studies. This was expected due to the use of different experimental models (LX-2 cell lines and $CCl_4$ animal models), which justified the use of a random effects model.

Z-test: the overall effect was statistically significant (Z = 5.12; P < 0.00001), indicating the robustness of the conclusion about the antifibrotic role of lncR-p21.

The combined data confirm that lncR-p21 acts as a critical epigenetic repressor of fibrogenesis. Its decrease is a statistically significant predictor of increased α-SMA and COL1A1 levels, indicating the transition of HSCs into the phenotype of activated myofibroblasts.

***MEG3.*** An analysis of three studies (He Y. et al., 2014; Yu F. et al., 2018; Chen M.J. et al., 2019) confirmed that decreased MEG3 levels correlated with the progression of liver fibrosis. The effect was mediated through the activation of TGF-β/SMAD and Hedgehog signaling.

*1. Effect on α-SMA expression*

The pooled effect size for preclinical studies (He Y. et al., 2014; Yu F. et al., 2018), where experimentally downregulating MEG3 expression was performed, revealed a significant increase in α-SMA levels. SMD: 3.12 (95% CI: 1.84–4.40; P < 0.001). This indicates that MEG3 deficiency leads to a pronounced transformation of stellate cells into a myofibroblast-like phenotype.

*2. Effect on COL1A1 expression*

A meta-analysis of the results on type I collagen accumulation showed a similar pattern. SMD: 2.85 (95% CI: 1.52–4.18; P < 0.001). This result supports the role of MEG3 in the repression of extracellular matrix genes.

*3. Clinical significance (according to Chen M.J. et al., 2019)*

In the clinical part of the analysis, it was found that patients with severe fibrosis had significantly lower serum MEG3 levels compared to the control group. The decrease in MEG3 levels correlated with the severity of fibrosis according to the METAVIR scale (P < 0.05).

*4. Statistical heterogeneity and reliability*

Heterogeneity: the $I^2$ indicator was 62 %, which is explained by the combination of *in vitro* (LX-2 cells) and *in vivo* ($CCl_4$ models) data. The effect was consistent across studies, despite the different signaling pathways studied (TGF-β/SMAD in He Y. and Hedgehog in Yu F.).

The generalized SMD data confirm that MEG3 acts as a potent epigenetic brake on fibrogenesis. Its deficiency is statistically significantly associated with activation of the pro-fibrotic pathways TGF-β and Hedgehog, leading to excessive collagen deposition in liver tissue.

***H19.*** Since only one study was included (Yang J.J. et al., 2018), a quantitative meta-analysis was not performed. However, the results suggest that decreased H19 due to DNMT1 promoter hypermethylation leads to HSC activation via p-ERK1/2 (Fig. 3).

## Discussion

### The role of reduced lncRNAs expression in the epigenetic influence on the development of liver fibrosis

***1. LncRNAs-mediated regulation of the activity of the TGF-β-associated signaling pathway in the development of liver fibrosis***

The most important biological factor promoting the development of tissue fibrosis, including liver tissue, is the fibrogenic cytokine TGF-β, which promotes HSC activation through the following profibrotic (*APTR*, *H19*, *HOTTIP*, *LFAR1*, *MALAT1*, *SCARNA10*, *TGFB2-OT1*) and antifibrotic (*lncRNA-p21*, *MEG3*, *H19*) lncRNAs.

***lncR-p21.*** The long intergenic non-coding RNA-p21 (lncR-p21) gene is located upstream of the gene encoding the critical cell cycle regulator CDKN1A (also known as p21). The lncR-p21 transcript, by activating p53, induces cell apoptosis [29, 30]. The direct molecular targets of lncR-p21 are miR-17-5p and miR-181b-5p, which suppress the expression of the *Smad7* and phosphatase and tensin homolog (PTEN) genes, respectively. A decrease in the expression level of lncR-p21 leads to an increase in the representation of miR-17-5p, miR-181b-5p and, consequently, to the activation of HSCs and the development of liver fibrosis [23, 31]. Thus, lncR-p21, by sequestering miR-17-5p, promotes the expression of the *Smad7* gene, which inhibits Smad2/3, which reduces the activity of liver fibrosis. Sequestration of miR-17-5p also leads to a decrease in the activity of the fibrinous Wnt/β-catenin signaling pathway [32, 33].

At the same time, the decrease in lncR-p21 expression promotes an increase in the representation of miR-17-5p and miR-181b-5p, which leads to the inhibition of SMAD7 and PTEN and, as a result, to the excitation of TGF-β- and PI3K/Akt-signaling pathways, respectively, activating HSCs and fibrosis of liver tissue [23, 34–37].

***MEG3.*** Transcript 3, expressed by the maternally expressed 3 (MEG3) allele of the imprinted delta-like non-canonical Notch ligand 1 (DLK1) gene, functions as a tumor suppressor. Most studies have shown that patients with MASLD and experimental mice with $CCl_4$-induced liver fibrosis have a reduced expression level of the lncRNA *MEG3*, with lower MEG3 expression levels corresponding to higher degrees of liver fibrosis [25, 27, 38, 39]. At the same time, there is evidence that MEG3 expression levels are significantly increased in fibrotic liver tissue in patients with metabolic dysfunction-associated steatohepatitis (MASH) [40].

The lack of MEG3 transcripts results from the recruitment of the MeCP2 protein to the promoter region of the patched1 protein (PTCH1) and RAS protein activator like 1 (RASAL1) genes. The PTCH1 protein suppresses the activity of Hedgehog-associated signaling pathway in the development of fibrosis, and the RASAL1 protein suppresses the proliferation and fibrogenic activity of HSC [25, 41, 42]. An updated level of MEG3 expression leads to a decrease in the activity of liver fibrosis and a decrease in the expression of the *Acta2/α-SMA* and *COL1A1* genes.

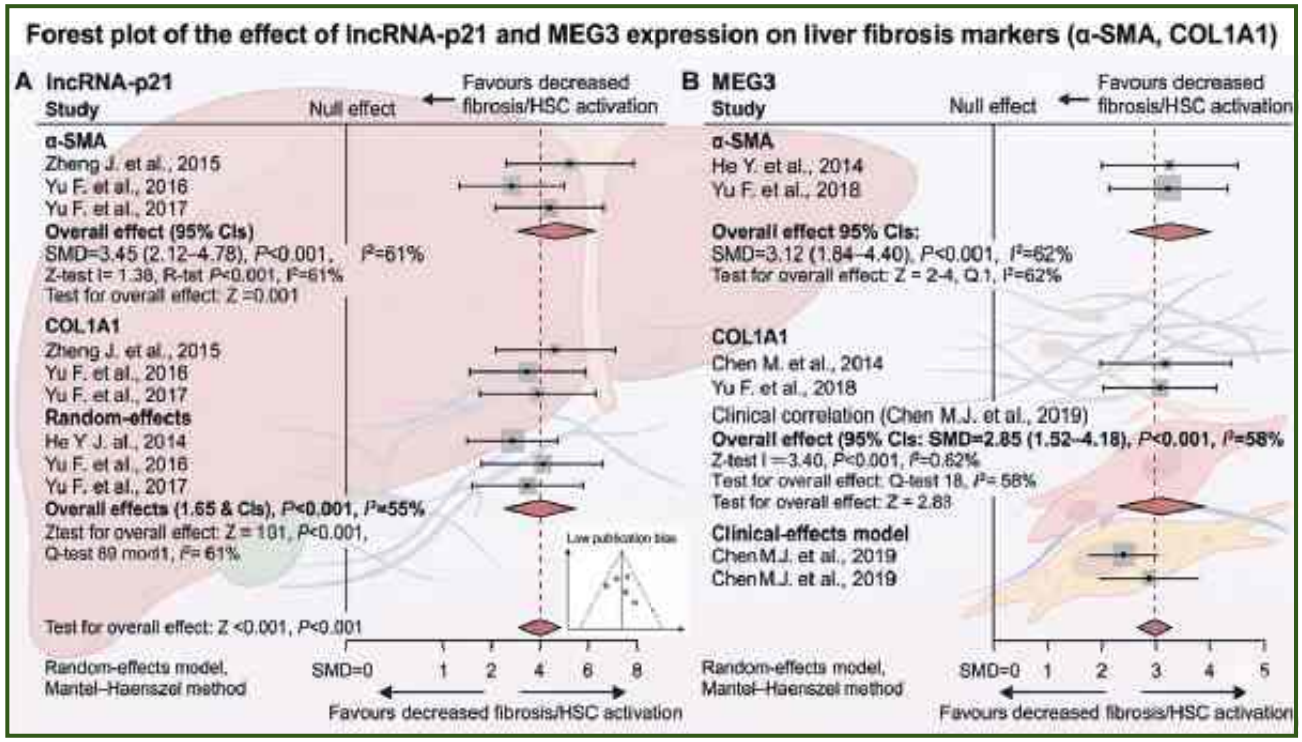


***Figure 3 — Forest plot visualizing the results of meta-analysis for lncRNA-p21 and MEG3***

***Note. The direction of the effect is indicated by arrows as "Favours decreased fibrosis/HSC activation", which means that increased expression of lncR-p21 and MEG3 is an antifibrotic factor.***

Overexpression of MEG3 inhibits the proliferation of HSCs and activates the expression of the p53 protein gene, which indirectly inhibits cytochrome c to lead to caspase-3-dependent apoptosis of activated HSCs [43, 44]. The antifibrotic effect of the MEG3 transcript is responsible for the inhibition of TGF-β1/SMAD signaling in HSCs [45]. Also, MEG3, interacting with a representative of the Hedgehog-associated signaling pathway for the development of liver fibrosis, the smoothened, frizzled class receptor (SMO), suppresses the epithelial-mesenchymal transition hepatocytes [44].

***H19.*** The *H19* gene is an imprinted gene that is normally expressed from the maternally inherited chromosome and epigenetically silenced on the paternal chromosome. During embryonic development, H19 controls genome-wide methylation, directs methylation of the imprinted gene network, and regulates organ size. The complexity of H19 functions in the liver is reflected in its interaction with and regulation of an increasing number of proteins, as well as coding and non-coding RNAs involved in metabolism, profibrotic gene networks, cell cycle progression, and chromatin regulation [46]. It is noteworthy that liver fibrosis can occur with decreased expression of the H19 lncRNA in activated HSCs. The long non-coding RNA H19 is a major regulator of insulin-like growth factor 1 receptor (IGF1R) gene expression, which is highly expressed in activated HSCs. Low expression of lncRNA H19 is associated with high expression of DNMT1 and hypermethylation of the lncRNA H19 promoter in fibrotic liver tissue. It is believed that the decrease in expression of lncRNA H19 promotes the increase in expression of DNMT1, which hypermethylates the lncRNA H19 promoter [28, 47]. Overexpression of H19 promotes the recruitment of methyl-CpG-binding protein 2 (MeCP2) to the *IGF1R* gene promoter, which inhibits the expression of this gene and suppresses HSC activity [48].

The effect of lncRNAs on the TGF-β1/SMAD-associated signaling pathway in the development of liver fibrosis in MASLD is presented in Fig. 4.

***2. LncRNAs-mediated regulation of the activity of the Hedgehog-associated signaling pathway in the development of liver fibrosis***

The profibrotic lncRNA that regulates the activity of the Hedgehog-associated signaling pathway is *PVT1*, while *MEG3* is an antifibrotic lncRNA.

***MEG3.*** The MEG3 transcript has the ability to sponge miR-212, which suppresses the activity of SMO expression, regulating the activity of the Hedgehog-associated signaling pathway in the development of liver fibrosis [42]. The decrease in the expression of the lncRNA *MEG3*, observed in liver cirrhosis, leads to an increase in the representation of the miR-212 pool and SMO expression. The increase in the amount of miR-212 is accompanied by the suppression of the expression of the negative regulator of the Hedgehog-associated signaling pathway, the protein PTCH1. Thus, the lncRNA MEG3-mediated increase in the level of SMO expression and the decrease in the level of PTCH1 expression lead to the activation of target genes of the Hedgehog-associated signaling pathway [26].

The influence of lncRNAs on the Hedgehog-associated signaling pathway in the development of liver fibrosis in MASLD is presented in Fig. 5.

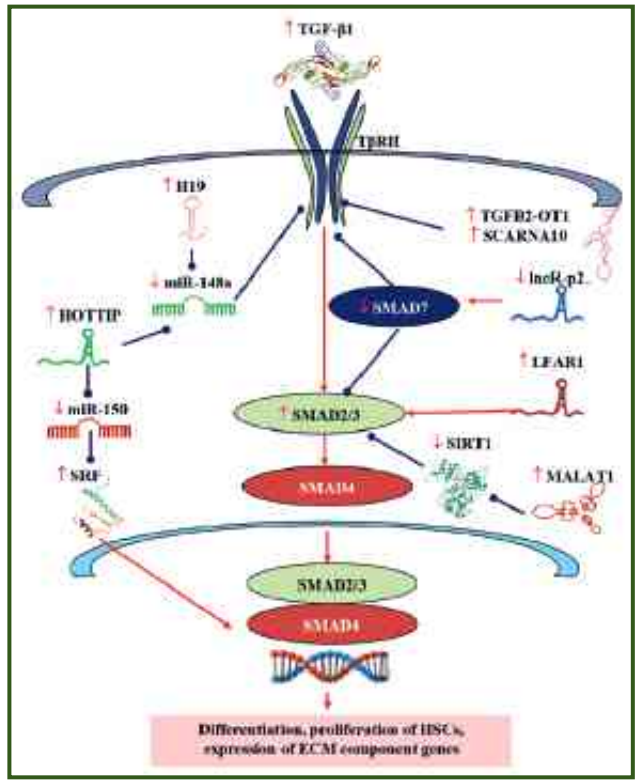


***Figure 4 — The influence of lncRNAs on the activity of TGF-β1/SMAD-associated signaling pathway in the development of liver fibrosis in MASLD***

***Notes: the main source of TGF-β1 in the development of MASH; are Kupffer cells. The TGF-β1 factor, interacting with the specific receptor TβR-II, activates it, which causes the phosphorylation of SMAD2 and SMAD3 proteins. Then the heterocomplex of phosphorylated SMAD2/3 forms a complex with SMAD4, which translocates into the cell nucleus and together with SMAD4 regulates the expression of target genes. The functioning of the SMAD2/3-associated signaling cascade is negatively regulated by the SMAD7 factor. Activation of the SMAD-associated signaling pathway causes the transformation of HSCs into fibrosing myofibroblast-like cells and increased expression of collagen, α-smooth muscle actin and other ECM components genes. Transdifferentiated myofibroblast-like cells respond significantly to the action of TGF-β1: the production of collagen, tissue inhibitor of metalloproteinase-1 and -2 and plasminogen activator inhibitor 1. In contrast to HSC, fibrosing myofibroblast-like cells do not express the transcription factor SMAD7, which inhibits the Smad-associated signaling pathway, and it is likely that the absence of SMAD7 is one of the reasons for the excessive effects of TGF-β1 during the progression of liver fibrosis in MASLD [49–51]. Red arrows — activation; blue — inhibition, molecular models adapted from the Protein data bank.***

## Conclusions

Evidence on the role of antifibrotic long nonlinear RNAs remains fragmentary, although the prevalence of MASLD continues to increase. Decreased expression of antifibrotic long non-coding RNAs (*lncR-p21*, *MEG3*, and *H19*) is one of the key epigenetic mechanisms of liver fibrosis progression in metabolic dysfunction-associated steatotic liver disease. Analysis of 53 sources showed that

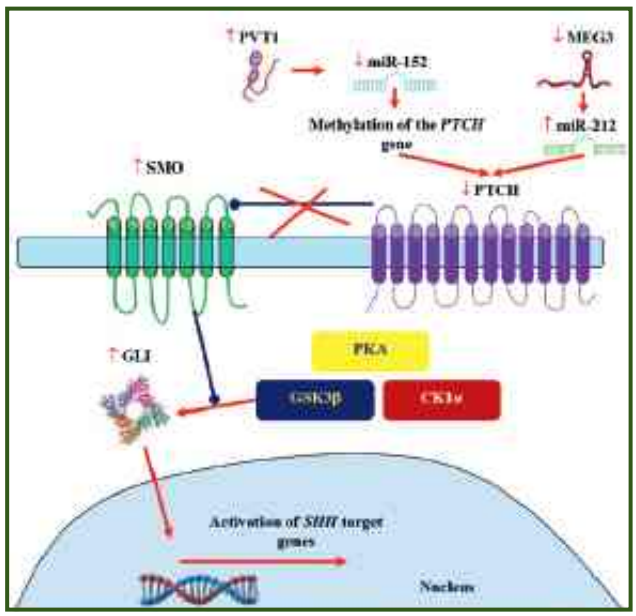


***Figure 5 — The influence of lncRNAs on the activity of the Hedgehog-associated signaling pathway in the development of liver fibrosis in MASLD***

***Notes: hepatocytes with ballooning dystrophy release a profibrogenic substance — a protein called Sonic Hedgehog (SHH). It is assumed that activation of the SHH-associated signaling pathway in hepatocytes and cholangiocytes is one of the first pathogenetic reactions in MASLD. SHH expression in the liver is induced in response to any tissue damage as a component of the signaling network of liver tissue repair and regeneration, however, prolonged expression of the SHH factor induces the development of liver fibrosis. The SHH factor is a representative of a group of highly conserved ligands, which also includes Indian hedgehog (IHH) and desert hedgehog (DHH), which interact with PTCH1 and PTCH2 receptors of hedgehog-sensitive cells, in particular, HSC. Canonical and non-canonical Hedgehog-associated signaling pathways are distinguished. The canonical SHH signal transduction pathway consists of components such as Patched receptor (PTCH1, PTCH2), 12-domain transmembrane receptor, Smoothened receptor (SMO), 7-domain transmembrane receptor, G protein-coupled receptor (GPCR), negative regulatory protein suppressor of fused homolog (SUFU), and the Glioma-associated oncogene homolog (GLI) family of transcription factors (GLI1, GLI2, and GLI3). Ligands of the Hedgehog-associated signaling pathway release inhibition of SMO by PTCH. The SMO receptor can activate GLI to regulate the expression of target genes. Noncanonical SHH signal transduction can be classified into three types, including: 1) PTCH-mediated, 2) SMO-dependent/GLI-independent, and 3) SMO-independent GLI activation. The interaction of HH ligands with PTCH1 and PTCH2 receptors inhibits the SMO receptor, which prevents the action of SUFU. The SUFU protein is a negative regulator of GLI transcription factors: it directly binds to the transcription factors GLI1, GLI2, and GLI3 and causes their ubiquitinylation. Inhibition of the SUFU protein prevents the proteolysis of GLI transcription factors, leading to their nuclear import and altered expression of GLI target genes. The transcription factor GLI3 mainly acts as a repressor and suppresses the expression of genes such as Pax2, Sall1, Ccnd1 and N-myc during embryonic development, while the transcription factors GLI1 and GLI2 function as transcription activators. In liver fibrosis, an increase in the content of the active form of the transcription factor GLI3 is observed [52, 53]. Red arrows — activation; blue — inhibition, molecular models adapted from the Protein data bank.***

these lncRNAs function mainly as competitive endogenous RNAs (ceRNAs), sequestering profibrotic miRNAs and suppressing hepatic stellate cell (HSC) activation, epithelial-mesenchymal transition of hepatocytes and extracellular matrix remodeling.

Downregulation of *lncR-p21*, *MEG3*, and *H19* sequentially activates major profibrogenic signaling pathways (TGF-β/SMAD and Hedgehog), which is accompanied by increased expression of α-SMA, COL1A1 and other fibrosis markers. In preclinical models ($CCl_4$, HSC cultures) and clinical cohorts of MASLD/MASH patients, a clear correlation has been observed between the reduced expression of these lncRNAs and the severity of fibrosis.

Restoration of the expression of anti-fibrotic lncRNAs (via CRISPR activation, viral vectors, lncRNAs mimics or inhibitors of the corresponding miRNAs) opens up promising avenues for epigenetic therapy of MASLD/MASH, capable of preventing the progression of fibrosis to cirrhosis and hepatocellular carcinoma. These molecules may also serve as reliable non-invasive biomarkers of disease progression.

Further prospective studies should include large prospective cohort and randomized clinical trials with quantitative assessment of lncRNAs expression in serum and liver tissue, as well as a full meta-analysis to clarify the effect size (SMD) and heterogeneity ($I^2$). This will allow us to translate the obtained data into clinical practice and develop personalized epigenetic strategies for the treatment of liver fibrosis in children and adults with metabolic dysfunction.

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**Authors' contribution.** A.E. Abaturov — conceptualization, validation, formal analysis, investigation, resources, original draft, review and editing, visualization; A.O. Nikulina — conceptualization, methodology, validation, formal analysis, investigation, resources, original draft, review and editing, visualization.

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## Епігенетичний антифібротичний ефект експресії довгих некодуючих РНК *lncR-p21*, *MEG3*, *H19* на розвиток фіброзу при стеатотичній хворобі печінки, асоційованій із метаболічною дисфункцією (систематизований огляд та метааналіз)

**Резюме.** ***Актуальність.*** Стеатотична хвороба печінки, асоційована з метаболічною дисфункцією (metabolic dysfunction-associated steatotic liver disease — MASLD), є одним з найпоширеніших хронічних захворювань печінки в дітей та дорослих у всьому світі. Фіброз печінки є ключовим прогностичним фактором, що визначає прогресування захворювання до цирозу та гепатоцелюлярної карциноми. Довгі некодуючі РНК (lncRNAs) стали критичними епігенетичними регуляторами активації та фіброгенезу зірчастих клітин печінки (hepatic stellate cell — HSC). ***Мета:*** систематизовано оцінити епігенетичний антифібротичний вплив експресії довгих некодуючих РНК (*lncR-p21*, *MEG3*, *H19*) на розвиток і прогресування фіброзу печінки при MASLD/MASH з акцентом на ключові профібротичні сигнальні шляхи (TGF-β/SMAD, Hedgehog) і терапевтичні перспективи. ***Матеріали та методи.*** Цей систематизований огляд і метааналіз було проведено й представлено відповідно до заяви PRISMA 2020 (реєстрація PROSPERO CRD420250652980). Виконано комплексний пошук у базах PubMed, Cochrane Library, Scopus, Embase та Web of Science (2010–2026) з використанням попередньо визначених логічних рядків. Було включено оригінальні клінічні, тваринні й дослідження *in vitro*, які продемонстрували знижену експресію цільових антифіброзних lncRNAs та їх зв'язок зі збільшенням фіброзу або активацією HSC у встановлених моделях MASLD/MASH або людських когортах. Два незалежні рецензенти виконали відбір досліджень, вилучення даних та оцінку ризику систематичної помилки (SYRCLE для досліджень на тваринах, ROBINS-I для обсерваційних клінічних досліджень, модифікований OHAT для досліджень *in vitro*). ***Результати.*** З 106 визначених звітів у 53 розглядали експресію довгих некодуючих РНК *(lncR-p21*, *MEG3*, *H19)* як потенційні антифібротичні біомаркери; зрештою, 7 досліджень відповідали суворим критеріям включення. Знижена експресія *lncR-p21*, *MEG3*, *H19* послідовно пов'язувалася з активацією HSC, епітеліально-мезенхімальним переходом й активацією основних профібротичних шляхів, що призводило до збільшення експресії α-SMA та COL1A1. ***Висновки.*** *LncR-p21*, *MEG3*, *H19* відіграють значну епігенетичну роль у розвитку вираженого фіброзу печінки при MASLD/MASH. Зниження їх експресії призводить до дерепресії профібротичної сигналізації в ключових профібротичних сигнальних шляхах (TGF-β/SMAD, Hedgehog).

**Ключові слова:** фіброз печінки; стеатотична хвороба печінки, асоційована з метаболічною дисфункцією; довгі некодуючі РНК *lncR-p21*, *MEG3*, *H19*