Review

Potential Role of miR-455-3p in Liver Fibrosis Among Metabolic Dysfunction-Associated Steatotic Liver Disease Patients

Mohammadjavad Sotoudeheian *

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Review

Potential Role of miR-455-3p in Liver Fibrosis Among Metabolic Dysfunction-Associated Steatotic Liver Disease Patients

Mohammadjavad Sotoudeheian

Faculty of Medicine, Iran University of Medical Sciences, Hemmat Exp, Tehran, Iran; javadsotoud@gmail.com

Abstract: Liver fibrosis, a progressive condition often linked to metabolic dysfunction-associated steatotic liver disease (MASLD), lacks specific biomarkers to accurately gauge disease progression and therapeutic response. Emerging research suggests that microRNAs, particularly miR-455-3p, may play a crucial role in modulating fibrosis-related pathways. This narrative review explores the potential of miR-455-3p as a biomarker and therapeutic target in liver fibrosis among MASLD patients. The miR-455-3p's effects on pathways, such as transforming growth factor-beta (TGF-β) signaling and extracellular matrix remodeling, both of which are pivotal in hepatic fibrosis. Additionally, the influence of miR-455-3p on hepatic stellate cell activation—a key process in fibrotic progression, should be considered. By challenging current perspectives, this review aims to elucidate the role of miR-455-3p in liver fibrosis, ultimately contributing to a deeper understanding of liver fibrosis mechanisms and highlighting the potential for innovative MASLD treatment strategies.

Keywords: NAFLD; miRNA; Diagnostic; TGF-β; hepatic stellate cells

Background

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), has emerged as a significant global health concern, closely linked to the rising prevalence of obesity and metabolic syndrome [1]. As MASLD progresses, it can lead to liver fibrosis, a critical stage in the disease spectrum that significantly impacts patient outcomes [2]. The early detection and accurate staging of liver fibrosis in MASLD patients remain challenging, highlighting the need for novel, non-invasive diagnostic tools [3].

In recent years, microRNAs have gained attention as potential biomarkers for various liver diseases, including MASLD and associated fibrosis [4]. Among these, miR-455-3p has shown promise in regulating key pathways involved in hepatic stellate cells (HSCs) activation and fibrogenesis [5]. However, the specific role of miR-455-3p in the context of MASLD-related liver fibrosis remains to be fully elucidated, presenting an opportunity for further investigation into its diagnostic capabilities in this patient population.

This study review the role of miR-455-3p in the context of MASLD-related liver fibrosis.

Liver Fibrosis in MASLD

Liver fibrosis, a key feature of advanced MASLD, affects a subset of patients with the condition [3]. It is estimated that about 7.5% of individuals with MASLD will progress to develop advanced fibrosis [6,7]. The pooled prevalence rates of advanced liver fibrosis and cirrhosis in the general population were 3.3% [8]. The presence and severity of liver fibrosis are crucial determinants of long-term outcomes in MASLD patients, as advanced fibrosis is associated with increased risk of liver-related morbidity and mortality [3].

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Epidemiological studies suggest that MASLD affects approximately 25-30% of the global adult population [9], with higher rates in Western countries and urban areas of developing nations [10]. The prevalence of MASLD increases with age and is more common in men than in women [11]. Among individuals with obesity or type 2 diabetes, the prevalence can reach up to 70-80% [12].

The disease burden of MASLD-related liver fibrosis is substantial. It is now one of the leading causes of liver cirrhosis, hepatocellular carcinoma, and liver transplantation in many countries [13]. The economic impact is also significant, with increased healthcare utilization and costs associated with managing the complications of advanced liver disease [14,15].

The Pathophysiology of Liver Fibrosis in MASLD

The pathophysiology of liver fibrosis in MASLD is complex and multifactorial, involving various cellular and molecular mechanisms. The progression from simple steatosis to fibrosis involves a series of events that lead to the activation of hepatic stellate cells (HSCs), the primary cell type responsible for extracellular matrix (ECM) production in the liver [2].

Lipotoxicity and oxidative stress play critical role in liver fibrosis progression during MASLD. The accumulation of lipids, particularly free fatty acids (FFAs), in hepatocytes is a hallmark of MASLD [16,17]. This lipid overload leads to lipotoxicity, which triggers several pathogenic processes. Moreover, mitochondrial dysfunction should be considered. Excess FFAs overwhelm the mitochondrial β-oxidation capacity, leading to the production of reactive oxygen species (ROS) [18–20]. This oxidative stress damages mitochondrial DNA and proteins, further impairing mitochondrial function. Furthermore, endoplasmic reticulum (ER) stress and lipid peroxidation could be responsible in this process. Lipid accumulation induces ER stress, activating the unfolded protein response (UPR) [17,21]. Prolonged UPR activation can lead to hepatocyte apoptosis. ROS interact with cellular lipids, forming lipid peroxidation products that can damage cellular structures and activate inflammatory pathways [22,23].

During inflammatory response, many cascades are engaged in liver fibrosis pathophysiology. Lipotoxicity and oxidative stress trigger an inflammatory response in the liver, characterized by activation of Kupffer cells, recruitment of inflammatory cells, the release of chemokine, NF-κB activation, and HSCs activation [24–26].

Kupffer cells as the liver-resident macrophages become activated and release pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [27]. Besides, the release of chemokines, e.g., MCP-1, CXCL10 leads to the infiltration of inflammatory cells, including neutrophils and lymphocytes [28]. NF-κB is a key transcription factor and is activated in hepatocytes and immune cells, promoting the expression of pro-inflammatory genes [29].

The activation of HSCs is the central event in liver fibrogenesis. Several factors contribute to HSC activation [30]. TGF-β, the most potent profibrogenic cytokine, is released by Kupffer cells and activated HSCs [31]. It binds to TGF-β receptors on HSCs, activating SMAD2/3 signaling pathways that promote collagen synthesis [32,33]. Platelet-Derived Growth Factor (PDGF) is a potent mitogen for HSCs is upregulated in MASLD, promoting HSC proliferation and migration [34]. Additionally, ROS directly activate HSCs and stimulate the production of fibrogenic mediators [35]. The activation of NADPH oxidases in HSCs further contributes to ROS generation and fibrogenic signaling [36]. Likewise, Hedgehog signaling pathway is activated in MASLD and promotes HSC activation and survival [37].

Extracellular matrix (ECM) remodeling plays a crucial role in the progression of liver fibrosis in MASLD, primarily driven by the activation and transdifferentiation of HSCs into myofibroblast-like cells. These activated HSCs become the primary source of excessive ECM deposition, significantly altering the liver's architecture and function [38]. The process is characterized by a marked increase in collagen production, particularly types I, III, and IV, along with other ECM proteins such as fibronectin and laminin [6]. Simultaneously, a complex interplay occurs between matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs). While some MMPs are upregulated to degrade normal ECM, the overexpression of TIMPs inhibits this degradation, ultimately favoring ECM accumulation [39]. Adding to this fibrotic cascade is the

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upregulation of lysyl oxidase, an enzyme responsible for cross-linking collagen fibers, which contributes significantly to the increased stiffness observed in the fibrotic liver. This intricate balance of increased ECM production, altered degradation, and enhanced cross-linking collectively drives the progression of liver fibrosis in MASLD, fundamentally changing the liver's structure and compromising its function [40,41].

Several interconnected molecular pathways contribute to the development and progression of liver fibrosis in MASLD, with the TGF-β/SMAD signaling pathway playing a central role. When TGF-β binds to its receptor, it activates SMAD2/3 through phosphorylation, leading to the formation of a complex with SMAD4 that translocates to the nucleus [32,33]. This complex interacts with various transcription factors to promote the expression of pro-fibrotic genes, including collagen and α-smooth muscle actin (α-SMA) [42]. Simultaneously, the PDGF signaling pathway is activated, binding to its receptor and triggering the Ras/MAPK and PI3K/Akt pathways, which promote HSC proliferation, migration, and survival, while also enhancing TGF-β effects on HSCs [43,44]. The Toll-Like Receptor (TLR) signaling pathway, particularly TLR4, is activated by gut-derived bacterial products, leading to NF-κB and JNK pathway activation, which further promotes inflammation and HSC activation [45,46].

Other significant pathways involved in liver fibrosis progression include the Wnt/β-catenin pathway, which promotes HSC activation and survival through β-catenin accumulation and nuclear translocation; the Notch signaling pathway, which interacts with TGF-β and Hedgehog pathways to amplify fibrogenic responses [47,48]; the JAK/STAT signaling pathway, activated by cytokines like IL-6, promoting hepatocyte survival and HSC activation through STAT3 activation [49,50]; and the Hippo/YAP pathway, whose dysregulation leads to increased YAP activity, promoting HSC activation and fibrogenesis through interaction with TEAD transcription factors [51–53]. These interconnected pathways collectively drive the complex process of liver fibrosis in MASLD, highlighting the multifaceted nature of the disease and the potential for targeted therapeutic interventions at various points in these signaling cascades.

Epigenetic mechanisms play a crucial role in the regulation of HSC activation and fibrogenesis in MASLD, influencing the progression of liver fibrosis through various molecular processes [54]. DNA methylation, particularly the hypermethylation of PPARγ, an anti-fibrotic transcription factor, contributes significantly to HSC activation. Histone modifications, including acetylation and methylation patterns, are altered in activated HSCs, affecting the expression of both pro-fibrotic and anti-fibrotic genes [55,56]. Additionally, microRNAs (miRNAs or miR) have emerged as important regulators of liver fibrosis in MASLD [4]. The dysregulation of these miRNAs contributes to the progression of liver fibrosis, highlighting the complex interplay between genetic and epigenetic factors in the pathogenesis of MASLD-related liver fibrosis. Understanding these epigenetic mechanisms provides potential targets for therapeutic interventions aimed at halting or reversing the fibrotic process [57,58].

The emerging concepts in MASLD-related liver fibrosis highlight the multifaceted nature of this condition and underscore the need for a holistic approach to its management. As research progresses, integrating these new insights into our understanding of MASLD pathophysiology will be essential for developing more targeted and effective treatments. Future studies should focus on elucidating the complex interactions between these various mechanisms and identifying key drivers of fibrosis progression in individual patients, paving the way for personalized therapeutic strategies in MASLD.

Liver Fibrosis Biomarkers

Early detection and accurate staging of liver fibrosis are crucial for effective management and improved patient outcomes. While liver biopsy remains the gold standard for fibrosis assessment, its invasive nature and potential complications have driven the search for non-invasive alternatives. Serum biomarkers have emerged as promising tools for the diagnosis, staging, and monitoring of liver fibrosis. This mini-review focuses on recent advances in serum biomarkers, with particular emphasis on galectins and miRNAs, as well as other emerging candidates [2,3,57].

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Galectins have emerged as a promising family of biomarkers for liver fibrosis, owing to their involvement in various biological processes, including inflammation and fibrosis. These β-galactoside-binding proteins have demonstrated significant potential in assessing and monitoring liver fibrosis progression across different etiologies of chronic liver disease [2].

Galectin-3, in particular, has garnered substantial attention as a biomarker for liver fibrosis [2]. Numerous studies have reported elevated serum levels of galectin-3 that correlate strongly with the severity of fibrosis in various liver diseases [59]. The utility of galectin-3 extends beyond initial diagnosis, as it has also demonstrated potential in monitoring fibrosis progression and assessing treatment response, making it a versatile tool in the management of chronic liver diseases [2].

Galectin-9 is another member of the galectin family that has shown promise as a biomarker for liver fibrosis. Research has revealed increased expression of galectin-9 in cirrhotic livers, with levels correlating closely with the stage of fibrosis. What makes galectin-9 particularly interesting is its ability to reflect both inflammatory and fibrogenic processes in the liver, providing a more comprehensive picture of disease activity and progression [60].

Galectin-1 has also been identified as a potential biomarker for liver fibrosis. This protein is upregulated in activated HSCs, which are key players in the fibrogenic process, and is found in increased amounts in fibrotic liver tissue [61,62]. Galectin-1 are associated with fibrosis in chronic hepatitis, suggesting its utility in assessing fibrosis progression in viral hepatitis [63,64].

Beyond the galectin family, other emerging serum biomarkers have shown promise in the assessment of liver fibrosis. Cytokeratin-18 (CK-18) fragments, particularly the M30 fragment, have gained attention as markers of hepatocyte apoptosis. These fragments are elevated in metabolic dysfunction-associated steatohepatitis (MASH) and correlate with the degree of fibrosis. The M30 fragment, which represents caspase-cleaved CK-18, has demonstrated particular promise in differentiating MASH from simple steatosis, addressing a significant diagnostic challenge in the management of MASLD [65,66].

Procollagen III N-terminal propeptide (PIIINP) is another biomarker that has shown utility in assessing liver fibrosis. This marker reflects active fibrogenesis and has been found to correlate well with the stage of fibrosis [67,68].

The emergence of these novel biomarkers, including galectins, CK-18 fragments, and PIIINP, represents a significant advancement in the non-invasive assessment of liver fibrosis. Their ability to reflect various aspects of the fibrogenic process, from hepatocyte injury to active matrix deposition, offers a more nuanced understanding of disease progression. As research continues, these biomarkers may play an increasingly important role in the diagnosis, monitoring, and management of chronic liver diseases, potentially reducing the need for invasive liver biopsies and improving patient care.

YKL-40, also known as Chitinase-3-like protein 1, is a glycoprotein secreted by activated macrophages and HSCs [69]. This biomarker has gained attention in the field of hepatology due to its elevated levels in various liver diseases. Studies have shown that YKL-40 concentrations in serum correlate well with the severity of liver fibrosis, making it a promising candidate for non-invasive fibrosis assessment. Its ability to reflect both inflammatory and fibrogenic processes in the liver provides valuable insights into disease progression and may offer advantages over traditional markers [69–71].

Osteopontin is a multifunctional protein that plays crucial roles in inflammation and fibrosis [72]. In the context of liver diseases, osteopontin has emerged as a potential biomarker for fibrosis assessment. Research has demonstrated that serum levels of osteopontin are associated with fibrosis stage in both MASLD and viral hepatitis [73–75]. This correlation extends across different etiologies of chronic liver disease, suggesting that osteopontin may serve as a versatile biomarker for fibrosis progression. Its involvement in multiple pathways related to liver injury and repair makes it an intriguing target for both diagnostic and therapeutic purposes [76,77].

Mac-2 binding protein glycosylation isomer (M2BPGi) has garnered significant attention as a novel biomarker for liver fibrosis. This glycoprotein undergoes alterations during the progression of liver fibrosis, making it a sensitive indicator of fibrotic changes. Numerous studies have demonstrated M2BPGi to be a reliable marker for fibrosis staging across various liver diseases. Its

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utility is particularly noteworthy in assessing fibrosis in chronic hepatitis C and NAFLD, two of the most common causes of chronic liver disease worldwide. The ability of M2BPGi to accurately reflect fibrosis stage without the need for invasive procedures has positioned it as a valuable tool in the clinical management of liver diseases [78].

Autotaxin is an enzyme involved in the production of lysophosphatidic acid, a potent mediator of various cellular processes including inflammation and fibrosis. In recent years, autotaxin has emerged as a promising serum biomarker for liver fibrosis [79]. Studies have shown that serum levels of autotaxin correlate strongly with fibrosis stage and liver stiffness measurements obtained through elastography [80]. One of the most intriguing aspects of autotaxin as a biomarker is its potential to differentiate cirrhosis from earlier stages of fibrosis [81]. This capability addresses a critical need in hepatology, as the transition to cirrhosis marks a significant turning point in disease progression and patient management. The ability to non-invasively identify this transition could have substantial implications for treatment decisions and prognostic assessments in patients with chronic liver diseases.

Furthermore, composite biomarker panels have emerged as a powerful approach to improving the diagnostic accuracy of liver fibrosis assessment [82]. By combining multiple biomarkers, these panels often outperform single markers in their ability to detect and stage fibrosis. PIIINP's value is further enhanced by its inclusion in several composite biomarker panels, such as the Enhanced Liver Fibrosis (ELF) score, which combines multiple markers to improve diagnostic accuracy. The ELF score, which combines procollagen III N-terminal propeptide (PIIINP), hyaluronic acid, and tissue inhibitor of metalloproteinase-1 (TIMP-1) [83]. The ELF score has been extensively validated for fibrosis assessment across various liver diseases. This recognition underscores its clinical utility and reliability in non-invasive fibrosis evaluation.

Another well-established composite panel is the FibroTest (FibroSure), which incorporates α2-macroglobulin, haptoglobin, apolipoprotein A1, γ-glutamyltransferase, and total bilirubin [82,84]. This panel has been widely validated for fibrosis staging, particularly in chronic hepatitis B and C, demonstrating its versatility across different etiologies of liver disease [85,86]. The NAFLD Fibrosis Score represents a targeted approach for non-alcoholic fatty liver disease, utilizing readily available clinical and laboratory parameters such as age, BMI, diabetes status, AST/ALT ratio, platelet count, and albumin. This score helps identify NAFLD patients at higher risk of advanced fibrosis, aiding in risk stratification and management decisions [87]. The Fibrosis-4 (FIB-4) index stands out for its simplicity and wide availability, combining age, AST, ALT, and platelet count to provide a quick assessment of fibrosis risk. Its ease of use and accessibility make it a valuable tool in various clinical settings [1,88].

The field of serum biomarkers for liver fibrosis continues to evolve rapidly, with several promising directions on the horizon. Multi-omics approaches, integrating data from proteomics, metabolomics, and transcriptomics, hold the potential to yield more accurate and comprehensive biomarker panels [89,90]. These integrative strategies may provide a more nuanced understanding of fibrosis progression and liver disease mechanisms. Liquid biopsy techniques, including the analysis of circulating tumor DNA, exosomes, and cell-free DNA, are emerging as powerful tools that may offer additional insights into fibrosis progression and liver disease etiology [91,92]. These minimally invasive approaches could potentially capture the dynamic nature of liver fibrosis more effectively than traditional static markers.

The application of artificial intelligence and machine learning to biomarker data represents another frontier in liver fibrosis assessment. Advanced algorithms have the potential to improve diagnostic accuracy and risk stratification by identifying complex patterns and relationships within biomarker data that may not be apparent through conventional analysis [93,94]. However, the development and implementation of these innovative approaches face several challenges. Standardization of assays and establishment of consistent cut-off values across different populations and disease etiologies remain crucial for widespread adoption. Extensive validation in large, diverse cohorts is necessary to ensure the generalizability of biomarker panels and AI-driven models [95]. The successful integration of these advanced biomarker strategies into clinical practice will require

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the development of clear guidelines for their use, as well as education and training for healthcare providers to effectively interpret and act upon the results. Addressing these challenges will be key to realizing the full potential of serum biomarkers in the non-invasive assessment and management of liver fibrosis.

Serum biomarkers represent a promising approach for non-invasive assessment of liver fibrosis. Galectins and miRNAs, along with other emerging biomarkers, offer potential advantages in terms of specificity, sensitivity, and ease of measurement. Composite panels that combine multiple biomarkers often provide improved diagnostic accuracy. While these biomarkers show great promise, further research is needed to fully validate their clinical utility across diverse patient populations and liver disease etiologies. As our understanding of liver fibrosis pathogenesis deepens and analytical technologies advance, we can expect the development of even more accurate and tailored biomarker strategies. The ultimate goal is to provide clinicians with reliable, non-invasive tools for early detection, accurate staging, and monitoring of liver fibrosis, thereby improving patient care and outcomes in chronic liver diseases.

The miRNAs as Liver Fibrosis Biomarkers

MiRNAs are small non-coding RNAs that regulate gene expression post-transcriptionally. Their stability in circulation and tissue-specific expression patterns make them attractive biomarker candidates [96]. The miRNAs have emerged as promising biomarkers for liver fibrosis due to their stability in circulation, ease of detection, and involvement in various stages of fibrogenesis [97]. These small non-coding RNAs play crucial roles in regulating gene expression and cellular processes associated with liver fibrosis, making them valuable indicators of disease progression and potential therapeutic targets [98].

Several miRNAs have been identified as potential biomarkers for liver fibrosis, with varying degrees of specificity and sensitivity [99]. Among the most extensively studied are miR-122, miR-21, miR-29 family members, miR-34a, and miR-155. Each of these miRNAs has demonstrated unique expression patterns and functional roles in the context of liver fibrosis [100,101].

miR-122 is the most abundant miRNA in the liver, accounting for approximately 70% of the total hepatic miRNA content [102]. Its expression is significantly altered in various liver diseases, including viral hepatitis, alcoholic liver disease, and MASLD. miR-122 is a liver-specific miRNA, decreased serum levels in advanced fibrosis. It is a potential marker for hepatocyte injury and fibrosis progression. In the context of liver fibrosis, serum levels of miR-122 have been found to correlate inversely with the stage of fibrosis. As liver damage progresses and hepatocytes are lost, circulating miR-122 levels decrease, making it a potential marker for advanced fibrosis and cirrhosis. However, the specificity of miR-122 as a fibrosis biomarker is limited by its elevation in acute liver injury, necessitating careful interpretation in the context of other clinical parameters [57,102,103].

miR-21 has gained attention as a pro-fibrotic miRNA that is upregulated in activated HSCs, the primary cell type responsible for extracellular matrix deposition in liver fibrosis [104]. Elevated serum levels of miR-21 have been associated with the progression of liver fibrosis in various etiologies, including chronic hepatitis B and C, as well as MASLD [57,105]. miR-21 is upregulated in activated HSCs and fibrotic liver tissue. This miR serum levels correlate with fibrosis stage in various liver diseases. Studies have shown that miR-21 levels correlate positively with fibrosis stage and can distinguish between mild and significant fibrosis with reasonable accuracy. The pro-fibrotic effects of miR-21 are mediated through its targeting of SMAD7, a negative regulator of TGF-β signaling, thus promoting HSC activation and fibrogenesis [106,107].

The miR-29 family, consisting of miR-29a, miR-29b, and miR-29c, has been extensively studied in the context of liver fibrosis [108,109]. These miRNAs are known to target multiple genes involved in extracellular matrix production, including various collagen isoforms. In liver fibrosis, the expression of miR-29 family members is typically downregulated, leading to increased collagen synthesis and fibrosis progression [109,110]. miR-29 family downregulated in fibrotic livers, correlating with increased ECM production. Serum levels may reflect fibrosis severity and treatment response [111]. Circulating levels of miR-29 have been explored as potential biomarkers, with some

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studies showing that decreased serum miR-29 levels correlate with advancing fibrosis stages [109,112]. The restoration of miR-29 expression has been proposed as a potential therapeutic strategy to attenuate fibrosis, highlighting the dual role of these miRNAs as both biomarkers and therapeutic targets [110,113].

miR-34a has emerged as a key player in liver fibrosis, particularly in the context of MASLD and MASH [4]. miR-34a is increased expression in MASLD/MASH and correlation with fibrosis severity [114]. This miRNA is involved in regulating cell cycle arrest, apoptosis, and senescence, processes that contribute to liver injury and fibrosis progression [115]. Elevated serum levels of miR-34a have been associated with the severity of liver fibrosis in MASLD patients, with some studies suggesting its potential as a biomarker for distinguishing MASH from simple steatosis [116]. The pro-fibrotic effects of miR-34a are mediated, in part, through its targeting of SIRT1, a key regulator of cellular metabolism and stress responses [4,117,118].

miR-155 is another miRNA that has shown promise as a biomarker for liver fibrosis. This miRNA plays a complex role in liver pathology, influencing inflammation, immune responses, and fibrogenesis [100,119,120]. Its inhibition can attenuate the liver fibrosis via STAT3 signaling [121]. Altered serum levels of miR-155 have been observed in patients with chronic liver diseases. The pro-fibrotic effects of miR-155 are attributed to its ability to promote the activation of Kupffer cells and HSCs, thereby liver fibrosis [122].

miR-200b, a member of the miR-200 family, has emerged as a significant player in liver fibrosis, particularly due to its involvement in the regulation of epithelial-to-mesenchymal transition (EMT) [123,124]. Moreover, in the context of liver fibrosis, miR-200a is typically downregulated, which contributes to the progression of fibrogenesis [125]. These miRNAs target key transcription factors involved in EMT, such as ZEB1 and ZEB2, which are critical for maintaining epithelial cell identity [126,127]. As liver fibrosis advances, the reduction in miR-200b levels allows for increased expression of these EMT-promoting factors, facilitating the transition of hepatocytes and cholangiocytes towards a more mesenchymal phenotype [124,128].

The Role of miR-455-3p in Liver Fibrosis

The role of miR-455-3p in liver fibrosis has emerged as a fascinating area of research, with potential implications for both diagnosis and treatment of this debilitating condition [129]. Recent studies have shed light on the complex interplay between miR-455-3p and various cellular mechanisms involved in the progression and reversal of liver fibrosis, particularly in the context of MASLD [5].

One of the most intriguing findings is the downregulation of miR-455-3p in activated HSCs and various hepatic fibrosis models. Wei et al. [5] demonstrated that miR-455-3p inhibits HSC activation by targeting heat shock factor 1 (HSF1), which is involved in the Hsp47/TGF-β/Smad4 signaling pathway. This discovery suggests that miR-455-3p acts as a natural brake on the fibrotic process, and its depletion may contribute to the progression of liver fibrosis in MASLD patients (**Figure 1**).

Further supporting this notion, You's research [130] revealed that miR-455-3p targets histone deacetylase 2 (HDAC2), another key player in liver fibrosis. The study found that miR-455-3p was downregulated in liver tissues of cirrhosis patients and fibrotic mouse models, while being upregulated during the reversal stage of hepatic fibrosis. This dynamic expression pattern hints at the potential use of miR-455-3p as a biomarker for both the progression and regression of liver fibrosis in MASLD patients (**Figure 1**).

Interestingly, the regulation of miR-455-3p itself appears to be under epigenetic control. You's [130] study demonstrated that DNA methyltransferases, particularly DNMT3b and DNMT1, mediate the hypermethylation of miR-455-3p promoter CpG islands in activated HSCs. This finding adds another layer of complexity to the role of miR-455-3p in liver fibrosis and suggests that epigenetic modulation could be a potential therapeutic approach for MASLD-related liver fibrosis.

The therapeutic potential of miR-455-3p is further underscored by studies exploring its delivery via exosomes. Shao's [131] research showed that exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSCs) enriched with miR-455-3p could attenuate inflammatory liver

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injury. This approach not only highlights the anti-inflammatory properties of miR-455-3p but also presents a novel delivery method that could be exploited for treating MASLD-related liver fibrosis.

Building on this, Zhou's [132] study demonstrated that hUC-MSCs could ameliorate hepatic fibrosis by upregulating miR-455-3p, which in turn suppresses p21-activated kinase-2 (PAK2). This finding expands our understanding of the downstream targets of miR-455-3p and reinforces its potential as a therapeutic target in liver fibrosis treatment (**Figure 1**).

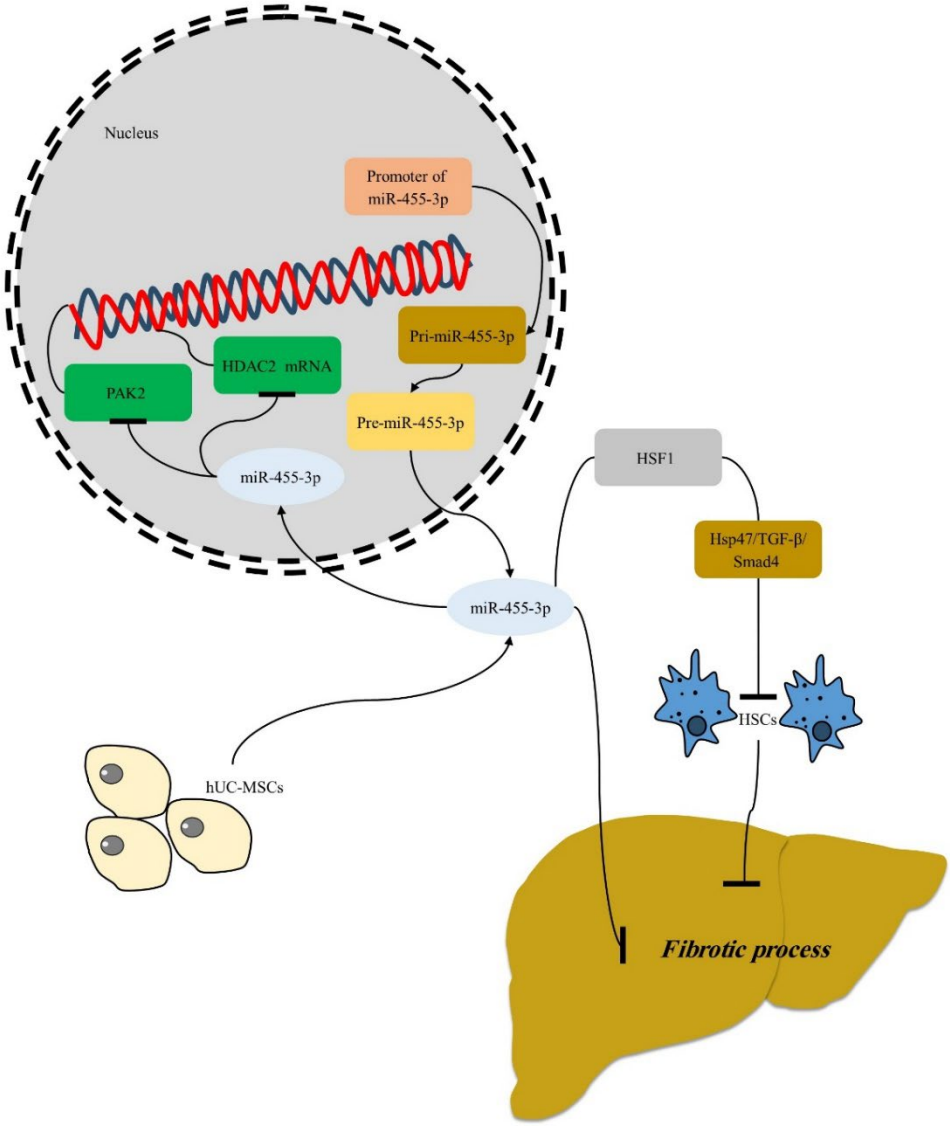

Figure 1. The schematic miRNA-455-3p interactions in liver fibrosis process.

However, despite these promising findings, several challenges remain in translating this knowledge into clinical applications for MASLD patients. The complex nature of miRNA regulation and the potential off-target effects of miRNA-based therapies need to be carefully considered. Moreover, the specific role of miR-455-3p in MASLD-related liver fibrosis, as opposed to other etiologies, requires further investigation to determine its diagnostic and therapeutic value in this particular patient population.

Future studies could explore the possibility of harnessing miR-455-3p in combination with other antifibrotic agents to achieve a synergistic effect that tackles fibrosis on multiple fronts. Longitudinal studies are essential to determine whether miR-455-3p expression changes correlate with clinical

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outcomes, potentially allowing miR-455-3p to serve as a biomarker not only for fibrosis but for broader MASLD-related disease stages.

Although miR-455-3p appears promising, miRNA therapies carry inherent risks due to their pleiotropic effects. Thus, assessing the safety and ethical implications of manipulating a miRNA like miR-455-3p is crucial before moving toward clinical trials. As with any novel therapy, miR-455-3p delivery systems must be scrutinized for safety, as inadvertent off-target effects could lead to unforeseen adverse outcomes in MASLD patients. The complex regulatory environment surrounding miRNA therapeutics necessitates thorough evaluation to ensure that any miR-455-3p-based treatment is both safe and effective for diverse patient populations.

Conclusion

In conclusion, the emerging role of miR-455-3p in liver fibrosis presents an exciting frontier in hepatology research, with potential implications in the pathogenesis of MASLD-related liver fibrosis and then for its diagnosis and treatment. As our understanding of this miRNA's function and regulation continues to grow, it may pave the way for novel diagnostic tools and targeted therapies that could significantly improve outcomes for patients with this challenging condition.

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