

Emerging role of non-coding RNAs in the progression of MASLD-driven hepatocellular carcinoma (Review)

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Abstract. Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide and a leading cause of liver-related morbidity and mortality. MASLD encompasses a pathological spectrum ranging from metabolic dysfunction-associated steatohepatitis to cirrhosis and hepatocellular carcinoma (HCC), making it the fastest-growing contributor to the global incidence of HCC. Non-coding RNAs (ncRNAs), once regarded as ‘genomic dark matter’, are increasingly recognised as key

regulatory molecules in a variety of liver diseases. However, their systematic involvement in the malignant progression from MASLD to HCC remains incompletely understood. Emerging evidence suggests that ncRNAs play critical roles in modulating the major pathophysiological processes underlying MASLD-driven HCC progression, including dysregulated lipid metabolism, chronic inflammation, oxidative stress, immune imbalance and gut microbiota disruption. The present review systematically examines the specific functions of major ncRNA classes, including microRNAs, long ncRNAs and circular RNAs, in the pathogenesis of MASLD-driven HCC. In addition, given their considerable diagnostic and therapeutic potential, the present review evaluates the prospects of ncRNAs as novel biomarkers and therapeutic targets to facilitate the early detection and precision treatment of MASLD-driven HCC.

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Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma; ncRNA, non-coding RNA; DAMPs, damage-associated molecular patterns; HSCs, hepatic stellate cells; MDSCs, myeloid-derived suppressor cells; SASP, senescence-associated secretory phenotype; SREBP-1c, sterol regulatory element-binding protein-1c; uPA, urokinase-type plasminogen activator; lncRNA, long ncRNA; LXR, liver X receptor; miRNA, microRNA; PPAR α , peroxisome proliferator-activated receptor α ; mTORC1, mTOR complex 1; m6A, N6-methyladenosine; NRF1, nuclear respiratory factor 1; mTOR, mechanistic target of rapamycin; IGF2, insulin-like growth factor 2; circRNA, circular RNA; FTO, fat mass and obesity-associated protein; ceRNA, competing endogenous RNA

Key words: non-coding RNA, metabolic dysfunction-associated steatotic liver disease, non-alcoholic steatohepatitis, hepatocellular carcinoma

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), affecting ~25% of the global population, is one of the most prevalent chronic liver diseases and is closely associated with metabolic dysregulation (1,2). The pathological hallmark of MASLD is excessive hepatic lipid accumulation, which may progress to metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis and hepatocellular carcinoma (HCC). MASLD is currently recognised as the fastest-growing aetiology of HCC worldwide (2). Early studies of MASLD largely relied on the ‘two-hit hypothesis’ to explain its pathogenesis. In this model, the first hit involves insulin resistance leading to hepatic steatosis, whereas the second hit comprises factors such as oxidative stress that promote inflammation and

fibrosis (3). However, subsequent investigations have demonstrated that the pathogenesis of MASLD is substantially more complex than suggested by the two-hit model, leading to the development of the ‘multiple-hit hypothesis’ (4).

The multiple-hit hypothesis departs from the linear framework of the two-hit model and instead proposes an integrated pathogenic network (4,5). According to this concept, multiple pathogenic factors, including insulin resistance, adipose tissue dysfunction, nutritional influences, gut microbiota dysbiosis and genetic and epigenetic alterations, act in a coordinated and dynamic manner rather than independently or sequentially. Through complex interactions, these factors collectively drive disease progression from simple steatosis to MASH, hepatic fibrosis and ultimately HCC. This framework plausibly explains the substantial interindividual variability in disease severity and progression observed among patients with MASLD. Since it more suitably reflects the multifactorial and dynamic nature of MASLD pathophysiology, the multiple-hit hypothesis has become widely accepted and has largely replaced the oversimplified two-hit model. Consequently, future preventive and therapeutic strategies are expected to adopt more comprehensive and individualised approaches that target the specific constellation of pathogenic factors present in each patient.

Non-coding RNAs (ncRNAs) comprise a diverse group of functional RNA molecules that lack protein-coding capacity, including long ncRNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs (circRNAs) (6). These molecules play critical roles in a wide range of human malignancies and other diseases (7-9), and growing evidence shows their pivotal regulatory roles in MASLD-driven HCC pathogenesis (10,11). Rather than being regarded as ‘junk’ RNA, ncRNAs are now recognised as key regulators of disease initiation and progression. By modulating gene expression, ncRNAs participate in virtually every stage of MASLD development, from hepatic steatosis and steatohepatitis to hepatic fibrosis, cirrhosis and eventual malignant transformation into HCC. Their regulatory mechanisms are highly complex, enabling them to function as either oncogenes or tumour suppressors, depending on the biological context.

The present review first summarises the epidemiological characteristics of MASLD-driven HCC and then discusses the underlying pathogenic mechanisms. It then reviews animal models of MASH-driven hepatocarcinogenesis, followed by an examination of the relationships between ncRNAs and both MASLD and HCC. The present review places particular emphasis on the roles of ncRNAs in the progression of MASLD-driven HCC. Research into ncRNAs has provided important insights into the pathogenesis of MASLD-driven HCC and has highlighted their potential as novel biomarkers and therapeutic targets. Although challenges remain, including functional redundancy among ncRNAs and the complexity of their regulatory networks, further elucidation of their molecular mechanisms will provide a robust foundation for the early diagnosis of MASLD-driven HCC and the development of precision therapeutic strategies.

2. MASLD-driven HCC

MASLD-driven HCC. MASLD-driven HCC refers to HCC that develops within the MASLD spectrum. Progression from

MASLD to HCC is a complex, multifactorial process involving chronic inflammation, oxidative stress, immune dysregulation, gut microbiota imbalance, lipotoxicity and glucotoxicity (12).

The earliest stage of MASLD is simple steatosis, now termed metabolic dysfunction-associated steatotic liver (MASL). Histopathologically, this stage corresponds to the entity formerly termed non-alcoholic fatty liver (NAFL), which is characterised by macrovesicular steatosis affecting >5% of hepatocytes in the absence of hepatocellular injury (13). This initial stage is primarily driven by persistent exposure to metabolic risk factors, including high-fat and high-sugar diets, obesity and type 2 diabetes (14). Notably, MASL is generally reversible, and management at this stage focuses on preventing disease progression through lifestyle interventions such as weight reduction and dietary modification.

A subset of patients subsequently progresses to MASH, a more advanced and severe pathological stage. The histological diagnosis of MASH requires hepatic steatosis involving >5% of hepatocytes, accompanied by lobular inflammation and hepatocyte ballooning, with or without fibrosis (15). At this stage, timely intervention may still reverse disease progression. However, persistent metabolic injury promotes the activation of fibrogenic signalling pathways, leading to progressive hepatic fibrosis. The final stage of fibrotic progression is cirrhosis, which is characterised by extensive architectural remodelling of the liver and confers a substantially increased risk of HCC (Fig. 1).

Notably, MASLD-driven HCC does not arise exclusively in cirrhotic livers. HCC may also develop in patients with advanced fibrosis who have not yet progressed to cirrhosis. In a cohort of 13,371 patients with MASLD-driven HCC, 37% of cases occurred without cirrhosis (16). These findings highlight the importance of maintaining vigilance for HCC risk even among patients with non-cirrhotic MASLD.

Epidemiology of MASLD-driven HCC. Although the incidence of numerous cancer types is declining worldwide, the burden of primary liver cancer continues to increase. According to GLOBOCAN 2024 global cancer statistics, ~843,000 new cases and 732,000 deaths from primary liver cancer were reported worldwide, ranking it among the leading causes of cancer-related incidence and mortality (17). Markov model-based projections further suggest that both the number of new cases and the incidence rate of primary liver cancer will continue to rise in both men and women through 2030 (18).

HCC is the predominant histological subtype of primary liver cancer, accounting for 75-85% of all cases (19). In the United States, for example, the annual number of newly diagnosed HCC cases is projected to increase from 5,160 to 12,240 by 2030, representing a 137% increase (20).

Cirrhosis remains the strongest independent risk factor for MASLD-driven HCC. A large cohort study of >290,000 individuals found that patients with MASLD and cirrhosis have an annual HCC incidence of 10.6 per 1,000 person-years, notably higher than in patients without cirrhosis (21). Furthermore, systematic reviews have shown that the annual risk of HCC development in cirrhotic individuals is at least 10-fold higher than that in non-cirrhotic individuals (22).

Nevertheless, cirrhosis is not a prerequisite for MASLD-driven HCC. Epidemiological studies indicate that

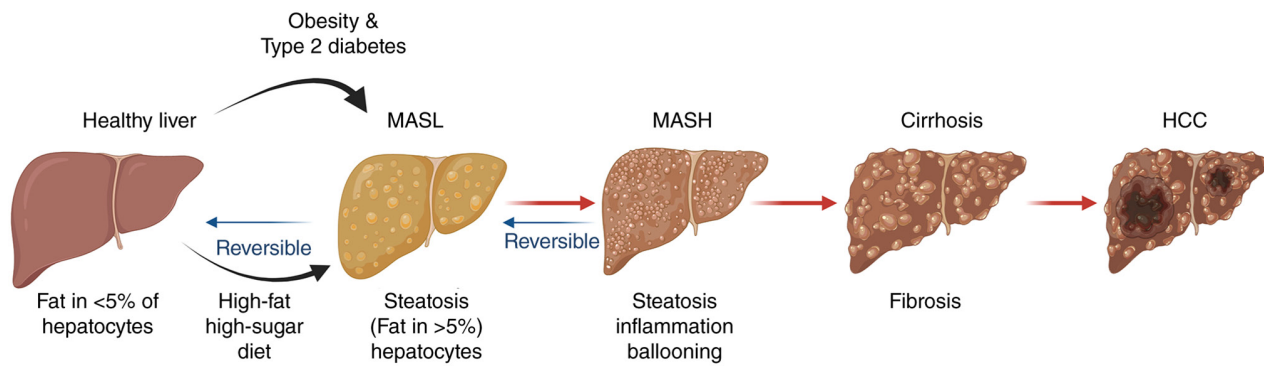


Figure 1. Schematic illustration of the progression from MASLD to HCC. Driven by risk factors such as obesity, type 2 diabetes mellitus and a high-fat and high-sugar diet, normal liver progresses to MASL, which is characterized by steatosis (>5% hepatocyte steatosis). It can also progress to MASH, characterized by inflammation and hepatocyte ballooning. Sustained damage will lead to fibrosis, cirrhosis and eventually progression to HCC. Notably, interventions may reverse the MASL and MASH phases. MASLD, metabolic dysfunction-associated steatotic liver disease; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis. Created with BioRender.com.

only ~50% of MASLD-driven HCC cases occur in the presence of cirrhosis, contrasting sharply with hepatitis C virus (HCV)-related HCC, where cirrhosis is present in the majority of cases (23). This distinctive feature poses challenges for risk stratification and surveillance strategies in patients with MASLD.

Although hepatitis B virus and HCV infections remain the leading causes of HCC worldwide (24), the burden of viral hepatitis-related HCC has gradually declined (25) owing to advances in antiviral therapies and the widespread implementation of vaccination programmes. By contrast, MASLD has emerged as the fastest-growing cause of HCC. An analysis of 2,106 patients with HCC revealed that, although viral hepatitis remained the dominant aetiology accounting for ~80% of cases, the proportion of HCC attributable to MASH increased by 68% over time (26). Furthermore, a large-scale study involving >900,000 patients with MASLD demonstrated that the disease significantly increases both the incidence of HCC and HCC-related mortality (27).

Metabolic disorders, particularly diabetes and obesity, are also major risk factors for HCC. The risk of developing HCC is ~87% higher in individuals with diabetes, and HCC-related mortality is increased by 1.88-fold in this population (28). Similarly, a meta-analysis reported a positive association between body mass index (BMI) and liver cancer risk, with risk increasing progressively as BMI rises (29). Notably, the prevalence of MASLD exceeds 50% among individuals with type 2 diabetes or severe obesity, further underscoring the close relationship between MASLD and metabolic dysfunction (30).

With ongoing socioeconomic development, lifestyle changes and the increasing prevalence of metabolic risk factors, the global burden of diabetes and obesity is expected to continue rising. Consequently, MASLD is likely to remain one of the fastest-growing causes of HCC worldwide.

Pathogenesis of MASLD-driven HCC

Chronic inflammation in MASLD-driven HCC. Chronic inflammation is widely recognised as a fundamental driver of tumour initiation and progression in numerous cancer types. For instance, persistent inflammation in inflammatory bowel disease is a major contributor to colorectal carcinogenesis (31).

Similarly, inflammation plays a central role in MASLD pathogenesis. Systematic reviews and meta-analyses show that elevated levels of inflammatory markers, including C-reactive protein, tumour necrosis factor- α (TNF- α) and interleukin (IL)-1 β , are significantly associated with both increased MASLD risk and greater disease severity, including steatohepatitis and liver fibrosis (32,33). These findings highlight chronic inflammation as a critical pathogenic mechanism underlying MASLD-driven HCC.

In MASLD and MASH, hepatic steatosis and metabolic stress, including insulin resistance, endoplasmic reticulum (ER) stress and mitochondrial dysfunction, together with gut microbiota dysbiosis and microbial metabolites such as lipopolysaccharide (LPS), collectively initiate chronic inflammatory responses (34,35). These stimuli activate innate immunity through damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns, which pattern-recognition receptors in the liver recognise. Activation of intracellular signalling pathways, including nuclear factor- κ B (NF- κ B), mitogen-activated protein kinase (MAPK) and Janus kinase (JAK)-signal transducer and activator of transcription (STAT), promotes production of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6, along with chemokines including C-C motif chemokine ligand (CCL) 2/monocyte chemoattractant protein-1 and CCL5 (36,37).

Activation of the NF- κ B pathway represents a pivotal mechanism driving inflammation and disease progression in MASLD (4,38). After pathway activation, TNF- α binds its receptor, recruits adaptor proteins and activates the I κ B kinase complex. Phosphorylation and degradation of I κ B α allow NF- κ B nuclear translocation, activating the transcription of genes encoding pro-inflammatory cytokines and chemokines (39). These mediators further sustain NF- κ B activation, establishing a positive feedback loop characterised by TNF- α production, immune-cell recruitment and subsequent amplification of inflammatory signalling. Furthermore, NF- κ B-C-X-C chemokine (CXC) receptor type 4 and 7 axis-mediated Toll-like receptor (TLR) 3 and TLR4 signalling has been implicated in the progression from MASH to HCC (40). An experimental study has shown that Huazhi Fugan Granule attenuates liver injury in MASLD models by suppressing TNF- α and NF- κ B signalling (41). Consequently,

the NF- κ B pathway has emerged as a promising therapeutic target for MASLD.

Chemokines promote the recruitment of circulating immune cells into the liver. Within the chronic inflammatory microenvironment, infiltrating monocytes differentiate into macrophages and polarise toward the pro-inflammatory M1 phenotype. These cells release additional inflammatory mediators, including TNF- α , IL-1 β and IL-6, thereby exacerbating inflammation and hepatocellular injury (42). IL-6 binding to its receptor activates JAK, which phosphorylates and activates STAT3. Activated STAT3 subsequently induces downstream pathways associated with resistance to apoptosis, enhanced proliferation, invasion, metastasis, angiogenesis and therapeutic resistance (43). Persistent STAT3 activation is recognised as a key driver of HCC initiation and progression (44).

Macrophage polarisation also contributes to disease evolution. Although M2 macrophages can suppress M1-mediated inflammatory activity by inducing programmed cell death, persistent inflammatory stimulation in MASH may lead to dysregulated immune responses and aberrant tissue repair, ultimately promoting fibrosis and establishing a pro-tumorigenic microenvironment (45). In addition, neutrophils contribute to hepatic injury by releasing proteases and neutrophil extracellular traps, further amplifying inflammation and tissue damage (46,47).

A critical event in the progression to fibrosis and cirrhosis is the activation of hepatic stellate cells (HSCs), which secrete large quantities of extracellular matrix (ECM) components (48). Fibrosis and cirrhosis are well-established risk factors for HCC development (49). Beyond their fibrogenic role, activated HSCs secrete pro-inflammatory cytokines and chemokines that recruit additional immune cells and sustain the inflammation-fibrosis cycle. HSC-derived matrix metalloproteinases (MMPs) further facilitate tumour cell migration, invasion and immune evasion (50,51). Consequently, HSCs have attracted considerable interest as potential therapeutic targets in liver cancer (52). Nevertheless, the precise mechanisms governing HSC activation and functional regulation remain incompletely understood, and targeted drug-delivery strategies directed at HSCs require further optimisation (53).

Overall, chronic inflammation is a central driver of progression from MASLD to HCC. Persistent activation of signalling pathways such as NF- κ B and JAK-STAT promotes sustained production of pro-inflammatory cytokines and chemokines, leading to continuous immune-cell recruitment and M1 macrophage polarisation. Simultaneously, activated HSCs contribute to ECM deposition, fibrosis and cirrhosis while fostering a pro-tumorigenic microenvironment that supports tumour-cell migration and immune evasion. Collectively, these events establish a self-perpetuating cascade of inflammation, fibrosis and carcinogenesis that ultimately culminates in HCC development (Fig. 2).

Oxidative stress in MASLD-driven HCC. Mitochondria function not only as the cellular ‘powerhouse’ but also as a major source of reactive oxygen species (ROS). Under physiological conditions, oxidative phosphorylation produces ATP and is a fundamental mitochondrial function. However, this process involves a small degree of electron leakage (0.2–2%) from the electron transport chain (ETC), resulting in direct oxygen reduction and ROS generation (54). Although low

levels of ROS have important physiological and protective functions (55), excessive ROS production induces oxidative stress, leading to cellular injury, DNA damage and disease development (56).

In MASLD, hepatic steatosis-associated fatty acid accumulation increases mitochondrial metabolic burden and impairs ETC function. This dysfunction directly increases electron leakage and superoxide anion generation. In addition, altered mitochondrial membrane fluidity may further exacerbate electron leakage, initiating oxidative stress and cellular damage (57). More notably, lipid overload, particularly excess saturated fatty acids and cholesterol, induces ER stress and the accumulation of unfolded proteins. Activation of ER stress and the unfolded protein response (UPR) generate large amounts of ROS. Concurrently, ER stress, for example through activation of the inositol-requiring enzyme 1 α pathway, disrupts the function of the sarco/ER Ca²⁺-ATPase pump, resulting in leakage of ER calcium stores. The subsequent influx of Ca²⁺ into mitochondria impairs mitochondrial function and further amplifies ROS production (58). Consequently, a self-perpetuating cycle develops between ER stress and mitochondrial dysfunction, leading to sustained oxidative stress.

Excessive ROS attack polyunsaturated fatty acids, generating cytotoxic lipid peroxidation products, including 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). These products directly contribute to MASH progression and, together with ROS, induce damage to mitochondrial DNA (mtDNA). Since mtDNA encodes essential components of the respiratory chain, its impairment further compromises ETC function and promotes additional ROS production (59). This process establishes a pathological positive feedback loop centred on mitochondrial dysfunction and ROS accumulation: Mitochondrial injury leads to increased ROS production, which results in lipid peroxidation, mtDNA damage and further mitochondrial dysfunction, culminating in further ROS generation. Continuous activation of this cycle sustains MASH progression and chronic inflammation. Furthermore, mtDNA acts as a key mitochondrial-derived DAMP. Following hepatocellular injury, mtDNA is released from damaged mitochondria and directly activates HSCs through receptors such as TLR9, thereby promoting liver fibrogenesis (60).

Oxidative stress-derived ROS also induce nuclear DNA damage. In hepatocytes, such damage may result in mutations of the tumour suppressor gene TP53 (59). Notably, mutant p53 not only loses its tumour-suppressive activity but may also acquire oncogenic functions and further enhance ROS production, thereby establishing an additional positive feedback loop that facilitates malignant transformation (61,62). In parallel, ROS function as potent activators of inflammatory signalling. By activating pathways such as NF- κ B and the NOD-like receptor protein 3 inflammasome, ROS stimulate the production of pro-inflammatory cytokines, including TNF- α and IL-6, thereby aggravating hepatic inflammation and hepatocellular injury (63).

As MASLD progresses to MASH and HCC, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) family is another major source of ROS, alongside mitochondria and the ER. NOX-mediated amplification of oxidative stress occurs through a characteristic three-step process. First, lipid peroxidation products such as 4-HNE and MDA act as

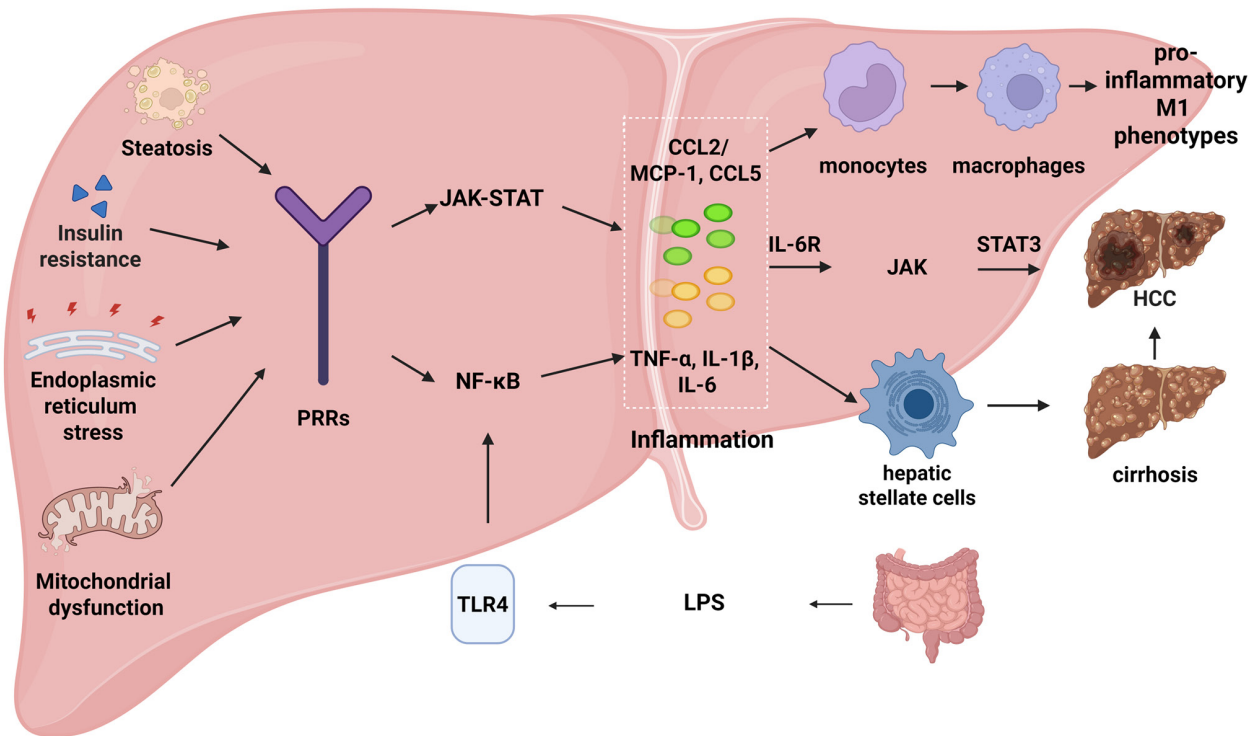


Figure 2. Schematic illustration of the mechanism by which chronic inflammation drives the progression of MASLD to HCC. Metabolic disorders (such as steatosis and insulin resistance), along with TLR4 and other pathways, activate JAK-STAT and NF- κ B signalling, increase proinflammatory factor production and recruit and polarize macrophages, driving inflammation and eventually progression to liver fibrosis, cirrhosis and HCC. MASLD, metabolic dysfunction-associated steatotic liver disease; HCC, hepatocellular carcinoma; TLR4, Toll-like receptor 4; JAK, Janus kinase; STAT, signal transducer and activator of transcription; NF- κ B, nuclear factor κ B; LPS, lipopolysaccharide; PRRs, pattern recognition receptors. Created with BioRender.com.

DAMPs and activate innate immune receptors, including TLRs and the receptor for advanced glycation end products. Second, receptor activation markedly upregulates NOX expression and activity, particularly NOX2 and NOX4, resulting in a burst of ROS production. Third, excessive ROS activate transcription factors such as NF- κ B, leading to the release of pro-inflammatory cytokines. These cytokines further stimulate NOX activity and ROS generation, establishing a self-sustaining positive feedback loop linking inflammation and oxidative stress that continuously exacerbates liver injury (64).

Overall, lipid overload in MASLD promotes ER stress and mitochondrial dysfunction, which mutually reinforce one another to sustain oxidative stress. Excessive ROS drive a vicious cycle centred on mitochondrial injury by inducing mtDNA damage, lipid peroxidation and TP53 mutations. Simultaneously, ROS activate NOX-dependent signalling pathways and establish a self-amplifying feedback network with inflammatory cytokines. Collectively, these interconnected mechanisms promote hepatic inflammation, fibrosis and malignant transformation, ultimately contributing to HCC development and progression (Fig. 3).

Immune dysregulation in MASLD-driven HCC. Under physiological conditions, the immune system maintains homeostasis through finely regulated bidirectional control mechanisms that enable the efficient elimination of pathogens and abnormal cells while preventing excessive tissue damage through immune tolerance. As a specialised immune organ, the liver contains a large and diverse population of resident immune cells, including Kupffer cells, natural killer (NK) cells and T lymphocytes, which collectively preserve hepatic

immune homeostasis and immune tolerance. Under normal circumstances, Kupffer cells remove blood-borne pathogens, such as bacteria and viruses, phagocytose senescent or damaged hepatocytes and support immune surveillance, immunoregulation and systemic immune tolerance (65).

However, during MASLD progression, chronic metabolic disturbances and lipotoxicity induce persistent hepatic inflammation, leading to profound alterations in the immune microenvironment. Kupffer cells preferentially polarise towards the pro-inflammatory M1 phenotype under chronic inflammatory conditions, producing high levels of cytokines and chemokines, including TNF- α , IL-1 β and IL-6. Activated Kupffer cells also secrete profibrogenic mediators, such as transforming growth factor- β (TGF- β) and platelet-derived growth factor, which induce HSC transdifferentiation into collagen-producing myofibroblasts and promote liver fibrosis (66,67).

Cluster of differentiation 8 (CD8)⁺ T cells play a crucial role in immune surveillance by recognising viral and tumour antigens presented on major histocompatibility complex class I molecules through their T-cell receptors. Upon activation, they eliminate infected or transformed cells by releasing perforin and granzymes, thereby protecting the host against malignant transformation (68). However, in MASLD, persistent antigenic stimulation within the chronically inflamed liver promotes CD8⁺ T-cell exhaustion. This dysfunctional state is characterised by reduced production of cytotoxic molecules and cytokines together with increased expression of inhibitory receptors, including programmed cell death protein 1, T-cell immunoglobulin and mucin domain-containing protein 3,

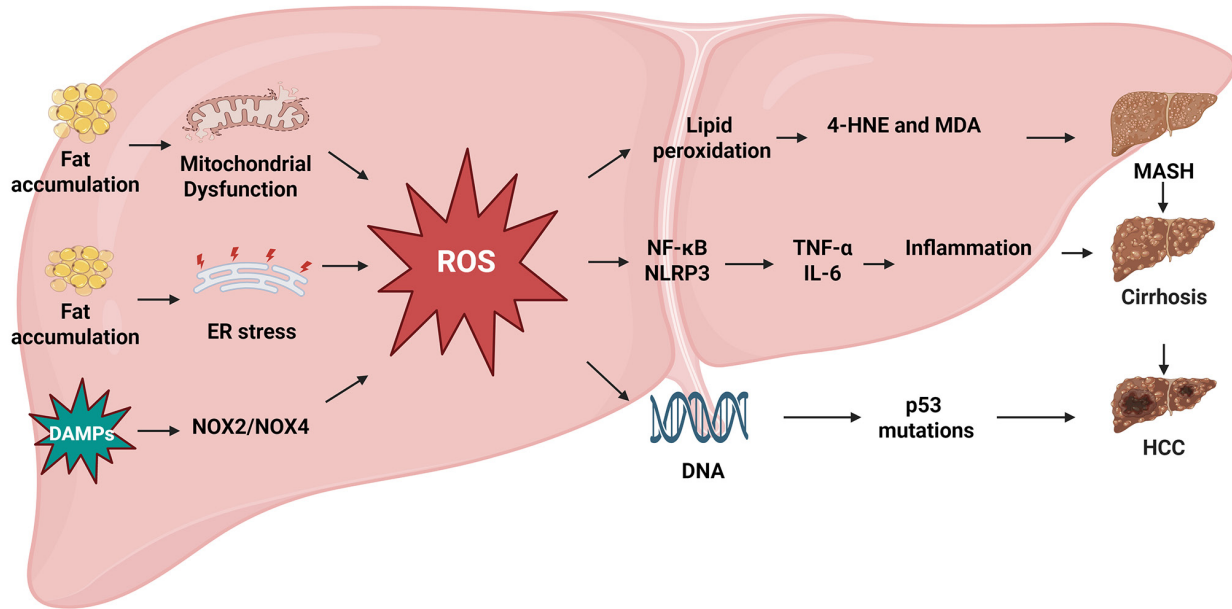


Figure 3. Pathogenic mechanism of oxidative stress in the progression of MASLD to HCC. Fat accumulation, coupled with mitochondrial and ER dysfunction, triggers ROS production. As a key hub, ROS trigger inflammation by activating the NF- κ B/NLRP3 pathway, leading to MASH. Furthermore, ROS cause lipid peroxidation and p53 mutations, which together promote progression from MASH to liver cirrhosis and HCC. MASLD, metabolic dysfunction-associated steatotic liver disease; HCC, hepatocellular carcinoma; ER, endoplasmic reticulum; ROS, reactive oxygen species; NF- κ B, nuclear factor κ B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; MASH, metabolic dysfunction-associated steatohepatitis; p53, tumour protein p53; DAMPs, damage-associated molecular patterns; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; IL, interleukin. Created with BioRender.com.

cytotoxic T-lymphocyte-associated protein 4 and lymphocyte activation gene 3 (69). Evidence from both human cirrhotic liver samples and experimental MASH models supports this exhausted phenotype (70).

Exhausted CD8⁺ T cells exhibit impaired antitumour activity and fail to eliminate preneoplastic and malignant cells efficiently, compromising immune surveillance and facilitating tumour immune escape. Furthermore, in obesity-associated MASH and cirrhosis, increased CD8⁺ T cell infiltration correlates positively with HSC activation, as reflected by elevated α -smooth muscle actin expression. Since activated HSCs are the principal source of collagen during hepatic fibrogenesis, this association suggests that CD8⁺ T cells directly contribute to fibrosis progression. Supporting this concept, experimental depletion of CD8⁺ T cells attenuates hepatic inflammation and suppresses HSC activation (71).

CD4⁺ T cells differentiate into distinct functional subsets according to the surrounding antigenic and cytokine environment, including T helper 17 (Th17) cells and regulatory T (Treg) cells. Under physiological conditions, immune homeostasis depends on a dynamic balance between pro-inflammatory Th17 cells and immunosuppressive Treg cells. However, in MASH, this equilibrium is disrupted. Treg cells expand substantially and infiltrate, further suppressing effector T-cell function and establishing an immune-tolerant microenvironment. Conversely, Th17 cells and their signature cytokine IL-17 promote inflammatory and fibrotic responses while directly facilitating tumorigenesis by stimulating angiogenesis and cellular proliferation (72).

Myeloid-derived suppressor cells (MDSCs) constitute a heterogeneous population of immature myeloid cells characterised by potent immunosuppressive activity. In MASLD, chronic inflammation drives marked MDSC expansion, with

cells recruited from the bone marrow and spleen to the liver in response to chemokines released by injured hepatocytes and activated Kupffer cells. MDSCs mediate immunosuppression through several complementary mechanisms. First, they deplete arginine, an amino acid essential for T-cell proliferation and function, leading to T-cell inactivation and cell-cycle arrest (73). Second, they generate ROS and reactive nitrogen species that disrupt T-cell signalling pathways and induce apoptosis (74). Third, they inhibit lymphocyte migration (75). Fourth, they actively promote the induction and expansion of immunosuppressive Treg cells (76). Collectively, these actions help establish a profoundly immunosuppressive microenvironment.

In addition, a study in murine models showed that MDSCs suppress T-cell and NK-cell function through ROS production mediated by NOX2 and inducible nitric oxide synthase (76). MDSCs can also promote macrophage polarisation towards an immunosuppressive M2-like phenotype and facilitate tumour growth by maintaining low levels of IL-12 secretion (77). Beyond their immunomodulatory functions, MDSCs support tumour progression through multiple non-immune mechanisms. These include promoting tumour angiogenesis through vascular endothelial growth factor secretion, enhancing nutrient supply to tumour tissues and remodelling the tumour microenvironment through the release of MMPs and additional cytokines, thereby facilitating tumour invasion and metastasis (78).

Overall, chronic inflammation during MASLD progression notably disrupts hepatic immune homeostasis. Kupffer cells acquire a pro-inflammatory, profibrotic phenotype; CD8⁺ T cells become exhausted; the Th17/Treg cell balance is disturbed; and MDSCs expand substantially. Together, these alterations establish a fibrogenic, immunosuppressive microenvironment that promotes immune evasion, fibrosis

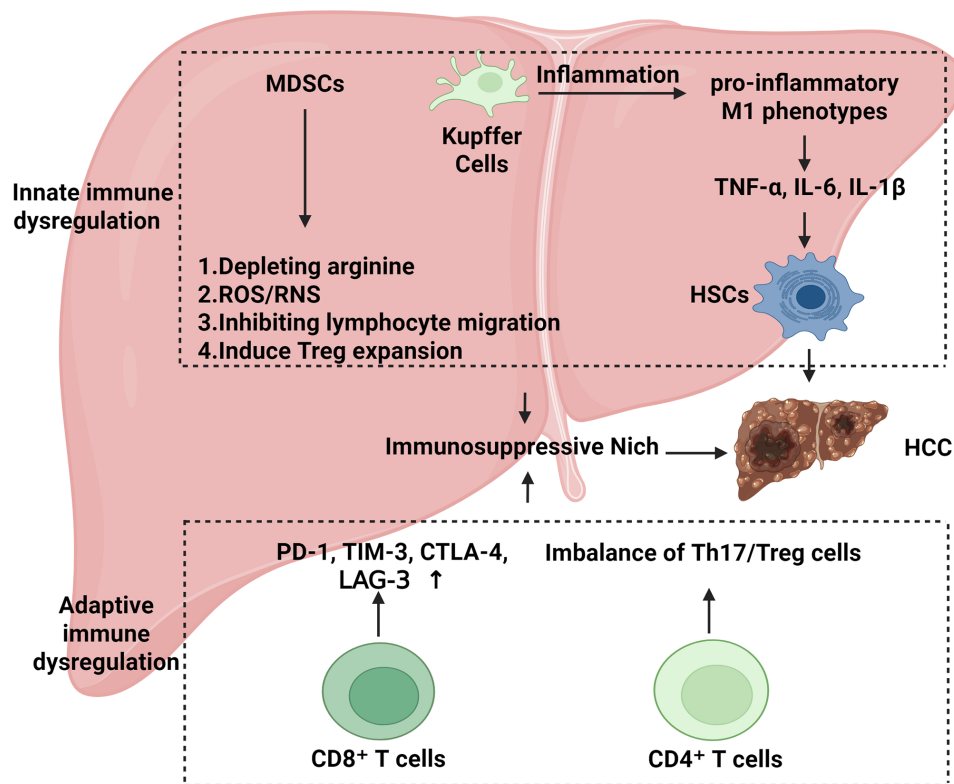


Figure 4. Schematic of how dysregulation of the liver immune microenvironment promotes HCC. After activation, Kupffer cells polarize into a pro-inflammatory M1 phenotype, release TNF- α and other factors and activate HSCs, driving inflammation and forming an immunosuppressive microenvironment. CD8⁺ T cells become exhausted, while CD4⁺ T cell helper function becomes imbalanced, leading to failed immune surveillance. These two pathways work together to provide the key conditions for hepatocellular carcinogenesis. TNF- α , tumour necrosis factor- α ; HSCs, hepatic stellate cells; CD4/8, cluster of differentiation 4/8; HCC, hepatocellular carcinoma; MDSCs, myeloid-derived suppressor cells; ROS, reactive oxygen species; RNS, reactive nitrogen species; IL, interleukin; PD-1, programmed cell death protein 1; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; LAG-3, lymphocyte activation gene 3; Th17, T helper 17 cells; Treg, regulatory T cells. Created with BioRender.com.

and tumour development, ultimately driving progression from MASLD to HCC (Fig. 4).

Gut microbiome dysbiosis in MASLD-driven HCC. The human gut harbours an immense microbial community comprising trillions of bacteria, viruses, fungi and other microorganisms that actively participate in numerous physiological processes. The gut and liver are connected by the portal vein, a direct, unidirectional and exclusive conduit that links them closely anatomically and functionally. Substances absorbed from the intestine, including nutrients, potentially harmful agents and bacterial metabolites, are transported via the portal vein to the liver for metabolic processing before entering the systemic circulation. Consequently, disruption of the gut microbiota can impair normal hepatic function, contributing to liver injury and related diseases.

The progression from MASLD to HCC is a complex, multistep process in which gut microbiota dysbiosis has emerged as a key driver. The principal mechanism involves dysbiosis-induced impairment of intestinal barrier function, which facilitates the translocation of bacterial metabolites, such as LPS and secondary bile acids, to the liver. This process triggers chronic inflammation and immune dysregulation, ultimately promoting HCC development (79). The intestinal barrier is a multilayered and highly coordinated defence system that regulates the selective absorption of nutrients and water while preventing the translocation of harmful substances, including bacteria, toxins and antigens, from the

gut lumen into the circulation. The intestinal barrier comprises four major components: i) The physical barrier, formed by intestinal epithelial cells and tight junctions, which prevents excessive permeability; ii) the chemical barrier, consisting of the mucus layer and antimicrobial secretions, which provides lubrication, separation and bactericidal activity; iii) the biological barrier, represented by the commensal microbial community that suppresses pathogen colonisation through competitive exclusion and nutrient competition; and iv) the immune barrier, which includes gut-associated lymphoid tissue and associated immune mediators that recognise and eliminate pathogens (80).

Dysbiosis is characterised by reduced beneficial bacteria, including short-chain fatty acid-producing species, leading to decreased production of key microbial metabolites such as butyrate. This reduction disrupts epithelial tight junctions and increases intestinal permeability (81,82). Simultaneously, the expansion of harmful bacterial populations and the production of toxic metabolites and enzymes, including ethanol and secondary bile acids, directly damage the mucus layer and intestinal epithelial cells (83,84), further disrupting physical and chemical barriers. Furthermore, harmful bacteria can occupy ecological niches, deplete nutrients and release toxins, further disturbing microbial homeostasis and weakening the biological barrier. The normal microbiota contributes to immune education by enabling the immune system to distinguish commensals from pathogens. Consequently,

dysbiosis may promote inappropriate immune responses against harmless antigens or commensal microorganisms, disrupting immune tolerance and impairing immune barrier function (85).

Following intestinal barrier disruption, large quantities of microbe-associated molecular patterns, particularly LPS derived from the cell wall of Gram-negative bacteria, enter the portal circulation. As a potent inflammatory stimulus, LPS binds to TLR4, activating the NF- κ B and MAPK signalling pathways. This activation promotes the release of proinflammatory cytokines, including TNF- α and IL-6, thereby driving hepatic inflammation and cellular injury (86). This mechanism is considered central to the transition from NAFLD to MASH.

In addition, secondary bile acids reaching the liver can induce HSC senescence and the formation of a senescence-associated secretory phenotype (SASP) (87), while also upregulating cyclooxygenase-2 (COX-2), a key enzyme involved in prostaglandin synthesis in HSCs (88). The SASP comprises a complex array of proinflammatory factors, chemokines, growth factors and proteases secreted by senescent cells. Through paracrine and autocrine signalling, these factors influence neighbouring cells and help establish a tumour-promoting microenvironment. An animal study has demonstrated that hepatic SASP activity markedly promotes HCC development (89). COX-2 is highly expressed in multiple malignancies and contributes to tumour cell proliferation, angiogenesis, immune evasion and metastasis (90). In MASH-driven HCC, COX-2-derived prostaglandin E2 can suppress antitumour immune responses, thereby promoting tumour progression (91).

Given the pivotal role of the gut microbiota in the initiation and progression of MASLD and its transition to HCC, therapeutic strategies targeting the gut microbiota represent a promising clinical approach. A previous review has systematically summarised preclinical and clinical studies evaluating microbiota-targeted interventions in MASLD, MASH and HCC, including probiotics, prebiotics, dietary interventions, faecal microbiota transplantation and antibiotics (92). These approaches have shown benefits for intestinal barrier integrity, inflammation and disease progression. However, limitations remain, including small sample sizes, incomplete mechanistic understanding and uncertain long-term efficacy. Further investigation is therefore required to optimise and validate these therapeutic strategies. Overall, the progression from MASLD to HCC is a complex, multistep process in which gut microbiota dysbiosis plays a central pathogenic role (Fig. 5).

Role of lipotoxicity and glucotoxicity in MASH and HCC development. Lipotoxicity is a pathological process in which the abnormal accumulation of toxic lipid species in organs and tissues leads to cellular dysfunction and, ultimately, cell death (93). As a major target organ of lipotoxicity, the liver normally esterifies free fatty acids (FFAs) with glycerol to form triglycerides, which are safely stored within lipid droplets under physiological conditions. However, when FFA influx exceeds the hepatic storage capacity, excess FFAs are diverted into non-esterification pathways, generating a range of harmful lipid derivatives (94).

Palmitic acid is a saturated fatty acid that the liver can synthesise *de novo*. Under physiological conditions, palmitic

acid synthesis occurs in the cytoplasm, where fatty acid synthase (FASN) converts acetyl-CoA and malonyl-CoA into palmitic acid. This multistep process requires NADPH and proceeds through sequential condensation, reduction and dehydration reactions (95). Physiological levels of palmitic acid are essential for normal cellular function. However, under pathological conditions, including insulin resistance, obesity and high-fat diets, excessive palmitic acid accumulation can transform palmitic acid into a potent lipotoxic molecule that disrupts ER lipid homeostasis, impairs protein folding and induces ER stress. Mechanistically, UPR activation contributes to insulin resistance and hepatic steatosis through its central role in cellular stress regulation (96). In addition, palmitic acid induces mitochondrial membrane depolarisation, abnormal mitochondrial fission, impaired ATP production and suppression of autophagy, resulting in the accumulation of dysfunctional mitochondria. Palmitic acid-induced oxidative stress and calcium overload trigger opening of the mitochondrial permeability transition pore, initiating caspase activation and apoptosis (97). An experimental study has demonstrated that mitochondria-targeted antioxidants can interrupt this process, thereby alleviating ER stress and cell death (98). Furthermore, palmitic acid activates pattern-recognition receptors, including TLR4, thereby stimulating inflammatory pathways such as NF- κ B and promoting hepatocyte secretion of proinflammatory cytokines, including TNF- α and IL-1 β . These events recruit and activate immune cells, contributing to MASH development (99).

The accumulation of other toxic lipids, including ceramides and free cholesterol, further promotes ER stress, oxidative injury and mitochondrial dysfunction, ultimately leading to hepatocyte death (100). A critical mechanism underlying MASH progression involves immune cell activation by DAMPs released from dying hepatocytes, resulting in persistent inflammation that exacerbates disease progression. Sustained inflammation activates HSCs, promoting collagen deposition and the development of hepatic fibrosis and cirrhosis (101). With ongoing DNA damage and dysregulated cellular proliferation, these pathological changes may ultimately culminate in HCC.

Glucotoxicity refers to the progressive cellular and tissue injury caused by chronic hyperglycaemia and its associated metabolic disturbances, including hyperinsulinaemia and insulin resistance, ultimately resulting in dysfunction and cell death. Its central mechanism involves disruption of metabolic homeostasis rather than a direct toxic effect of glucose itself. As MASLD progresses to HCC, glucotoxicity contributes through several interconnected mechanisms. First, it exacerbates lipid metabolic dysfunction. Sterol regulatory element-binding protein-1c (SREBP-1c), a key transcription factor regulating hepatic lipogenesis, promotes the expression of genes involved in fatty acid synthesis (102). Insulin activates SREBP-1c and thereby enhances hepatic fatty acid synthesis (103). Under hyperinsulinaemic conditions, excessive SREBP-1c activation markedly increases lipogenesis, worsening hepatic steatosis and lipotoxicity. Simultaneously, insulin resistance and hyperinsulinaemia suppress fatty acid oxidation, further promoting lipid accumulation within hepatocytes (104).

Second, chronic hyperglycaemia drives the formation of advanced glycation end products, a process closely associated

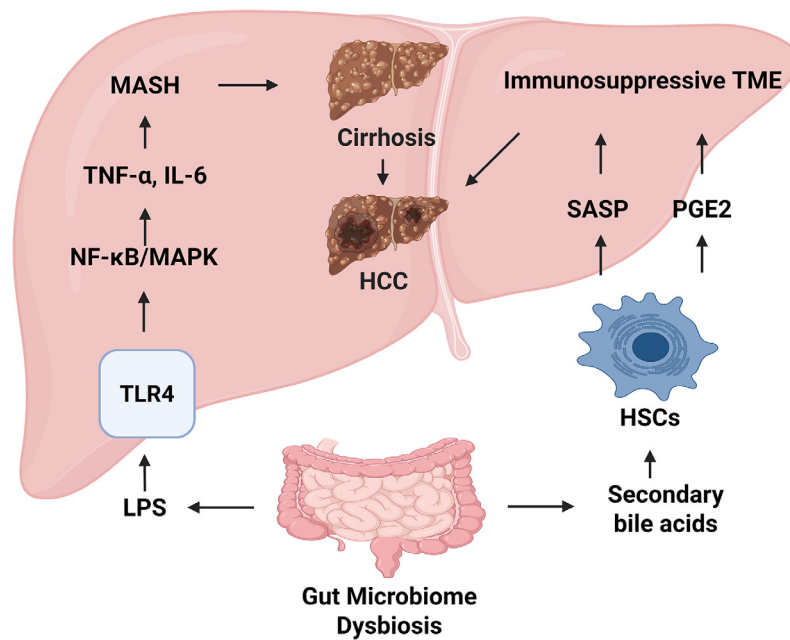


Figure 5. Mechanism by which gut microbiome dysbiosis triggers inflammation and fibrosis, leading to HCC development. Gut microbiota dysbiosis increases harmful products, such as LPS and secondary bile acids, which enter the liver through the portal vein. LPS can activate the TLR4 receptor on hepatocytes, trigger inflammatory signalling pathways such as NF-κB/MAPK and produce pro-inflammatory factors such as TNF-α and IL-6, driving progression from MASH to cirrhosis. In liver cirrhosis, activated HSCs secrete SASP and PGE2, which together create an immunosuppressive TME and ultimately promote HCC development. LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; MASH, metabolic dysfunction-associated steatohepatitis; HSCs, hepatic stellate cells; SASP, senescence-associated secretory phenotype; PGE2, prostaglandin E2; TME, tumour microenvironment; HCC, hepatocellular carcinoma. Created with BioRender.com.

with oxidative stress. Advanced glycation end products binding to receptors on hepatocytes and Kupffer cells activates multiple signalling pathways, notably NF-κB, MAPK and JAK/STAT, while also stimulating NOX activity. These events promote excessive ROS generation (105), thereby amplifying oxidative stress, inflammatory cytokine production and cellular injury, which collectively contribute to MASH development. In parallel, chronic inflammation further activates HSCs, accelerating the progression of hepatic fibrosis and cirrhosis. During hepatocarcinogenesis, the combined effects of hyperinsulinaemia and a proinflammatory microenvironment promote DNA damage, enhanced cellular proliferation and immune evasion. Collectively, these processes facilitate HCC development (106).

In summary, glucotoxicity contributes to the malignant progression of liver disease from MASLD to HCC through multiple mechanisms, including disruption of lipid metabolism, induction of oxidative stress and the promotion of chronic inflammation (Fig. 6).

Animal models of MASH-driven HCC. Due to the complex pathophysiology of MASLD, its precise pathogenic mechanisms remain incompletely understood, and effective therapeutic options remain limited. Animal models are indispensable tools for investigating disease mechanisms, evaluating therapeutic efficacy and screening potential drug candidates. Accordingly, appropriate MASLD models are essential for drug discovery, validation of novel therapeutic strategies and improving the understanding of the biological processes underlying MASH and MASH-driven HCC.

A variety of animal models have been developed to study MASLD, most of which are based on dietary

interventions (107). Among these, the Western diet model, characterised by high fat and high sugar intake, has been widely recommended (108). This model typically incorporates a diet containing high fat content (usually 40-45% of total caloric intake), elevated levels of sugars, particularly fructose and sucrose, and high cholesterol content (1-2%). It effectively recapitulates several features of human metabolic syndrome, including obesity, insulin resistance and diabetes, while reproducing the full histopathological spectrum of MASH, including hepatic steatosis, inflammation, hepatocellular ballooning and fibrosis. Following prolonged feeding for >12 months, male C57BL/6J mice may spontaneously develop HCC, making this model a benchmark for investigating the natural history of MASH-driven HCC (109).

Nevertheless, no animal model can fully reproduce all aspects of human MASH, and each model has inherent limitations. Although the Western diet model is widely used, some investigators have argued that it inadequately reproduces the immunosuppressive microenvironment that contributes to progression from MASH to HCC (110). Consequently, these researchers advocate the use of the major urinary protein promoter-driven urokinase-type plasminogen activator (MUP-uPA) transgenic model (111). The MUP-uPA model is considered one of the current reference models for studying MASH-driven HCC due to its spontaneous disease progression, accurate representation of the tumour immune microenvironment, conservation of relevant molecular pathways and capacity to predict therapeutic responses. However, this model is also subject to several limitations, including relatively slow tumour development, substantial tumour heterogeneity, inadequate reproduction of the intensity of human inflammatory responses, incomplete representation

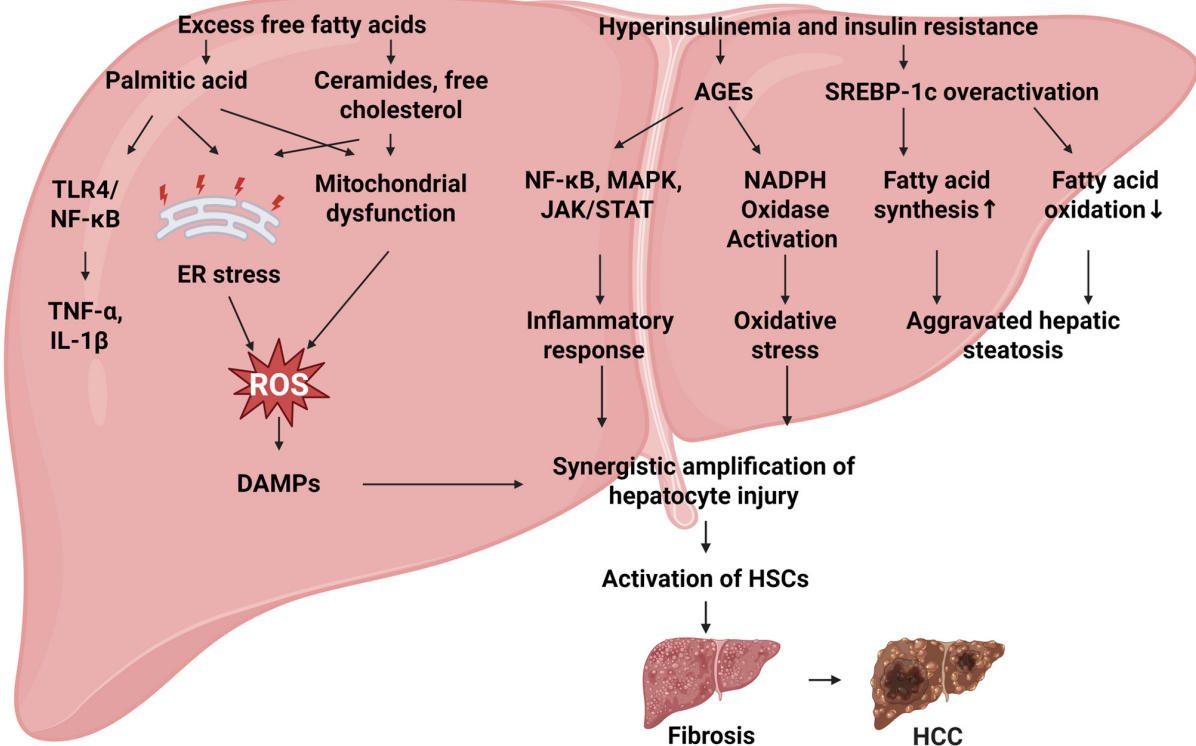


Figure 6. Schematic illustration of the key molecular mechanisms by which lipotoxicity and glucotoxicity drive the progression of MASLD to HCC. Excess FFAs (such as palmitic acid) and their derivatives (ceramide and free cholesterol) trigger a strong inflammatory response (production of $\text{TNF-}\alpha$ and $\text{IL-1}\beta$) by activating the TLR4/NF- κ B pathway and inducing ER stress. These stresses, together with hyperinsulinemia, increase ROS production and drive oxidative stress. Hyperinsulinemia and insulin resistance worsen hepatic steatosis by overactivating SREBP-1c and disrupting lipid metabolism (fat synthesis increases and fatty acid oxidation decreases). Damage signals (such as ROS and DAMPs) released by these three pathways synergistically amplify and jointly activate HSCs, ultimately driving liver fibrosis and HCC. MASLD, metabolic dysfunction-associated steatotic liver disease; HCC, hepatocellular carcinoma; FFAs, free fatty acids; $\text{TNF-}\alpha$, tumour necrosis factor- α ; $\text{IL-1}\beta$, interleukin-1 β ; TLR4, Toll-like receptor 4; NF- κ B, nuclear factor κ B; ER, endoplasmic reticulum; ROS, reactive oxygen species; SREBP-1c, sterol regulatory element-binding protein 1c; DAMPs, damage-associated molecular patterns; HSCs, hepatic stellate cells; MAPK, mitogen-activated protein kinase; JAK, Janus kinase; STAT, signal transducer and activator of transcription; AGEs, advanced glycation end products. Created with BioRender.com.

of the diversity of human disease subtypes, difficulties in recapitulating the human gut microbiome and dependence on transgenic uPA overexpression. Consequently, it may not fully reflect the natural pathogenesis of human disease.

At present, an ideal animal model capable of reproducing the entire spectrum of human MASH-driven HCC has not been established. Therefore, investigators should select the most appropriate model according to the specific scientific objectives and pathological features under investigation.

3. ncRNAs and MASLD

Classification and functional modalities of ncRNAs. ncRNAs are conventionally categorized according to two complementary frameworks: By functional role into housekeeping and regulatory ncRNAs or by transcript length into small ncRNAs (<200 nucleotides) and lncRNAs (≥ 200 nucleotides) (112,113). As a detailed account of ncRNA classification and biogenesis falls outside the scope of the present review, the reader is referred to dedicated summaries of this topic (112–114). Briefly, the classes most pertinent to hepatic pathophysiology are miRNAs (~22 nucleotides; mediators of post-transcriptional gene silencing), lncRNAs (RNA polymerase II transcripts that lack a significant open reading frame) and circRNAs, which are generated by back-splicing into covalently closed

loops and are thus highly stable and resistant to exonucleolytic degradation (114).

Although other ncRNA classes, including small nucleolar RNAs, PIWI-interacting RNAs and tRNA-derived small RNAs, have been implicated in liver pathophysiology and hepatocarcinogenesis (115,116), a recent systematic review of MASLD and MASH reported that, among 134 eligible preclinical studies, 96 focused on miRNAs, 38 on lncRNAs and 11 on circRNAs (117). These findings indicate that these three classes currently possess the strongest evidence base in the MASLD-driven HCC field. Accordingly, the present review focuses on the three ncRNA classes supported by the strongest evidence in MASLD-driven HCC.

Transcriptional regulation is a well-established functional modality of lncRNAs. Nuclear lncRNAs act as modular scaffolds or guides that recruit chromatin-modifying complexes, function as transcriptional decoys that sequester transcription factors from their cognate promoters and act either in cis on neighbouring genes or in trans at distal loci, while enhancer RNAs promote enhancer-promoter looping through chromatin-looping factors. As these classical paradigms have been reviewed extensively elsewhere, the reader is referred to dedicated summaries (118–121). In steatotic livers, this modality has direct pathophysiological relevance, as illustrated by several MASLD-specific examples: The lncRNA *Blnc1* serves

as a core component of the liver X receptor (LXR) transcriptional complex and licenses pathological hepatic lipogenesis by activating the SREBP-1c lipogenic program (122); the steroid receptor RNA activator (SRA) lncRNA facilitates hepatic lipid accumulation partly by directly activating insulin receptor gene transcription (123,124); H19, which is upregulated in MASLD, promotes a protumorigenic lipogenic programme through the H19/PTBP1/SREBP1 feed-forward loop and mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) signalling (125,126); and the circRNA-derived micropeptide circ-SLC9A6-126aa promotes hepatic lipid uptake by activating CD36 transcription in an H4K16ac-dependent manner (127). Numerous other lncRNAs couple epigenetic dysregulation to metabolic dysfunction by sustaining lipogenic transcription-factor networks or repressing tumour-suppressive programs (119,122).

Post-transcriptional regulation is the canonical functional modality of miRNAs, which are processed by Drosha/DGCR8 and Dicer and loaded into the RNA-induced silencing complex to repress target mRNAs through partial base pairing with their 3'UTRs (128). As single miRNAs co-ordinately regulate hundreds of transcripts, they act as network-level rheostats over hub metabolic and oncogenic pathways, a property of direct relevance to MASLD-driven HCC. miRNA networks calibrate lipogenesis, oxidative stress and inflammatory signalling in hepatocytes, with miR-21-5p promoting lipid accumulation and tumorigenesis via peroxisome proliferator-activated receptor α (PPAR α), miR-378 impairing fatty acid oxidation and loss of the liver-intrinsic tumour suppressors miR-223 and miR-122 accelerating MASLD progression and increasing the incidence of spontaneous HCC, respectively (129). Comparable post-transcriptional crosstalk also operates across ncRNA classes. circRNA_0046366 sponges miR-34a to relieve PPAR α -mediated suppression and enhance fatty acid β -oxidation (130), whereas GAS5 sponges miR-29a-3p to upregulate NOTCH2 and aggravate steatohepatitis (131), illustrating that competing endogenous RNA (ceRNA)-mediated derepression is a recurring post-transcriptional motif in MASLD progression.

Another functional modality involves assembling ribonucleoprotein complexes. Certain lncRNAs function as molecular scaffolds that physically bridge multiple proteins into complexes with distinct signalling outputs (120). In hepatic malignancy, for example, the lncRNA SNHG6 promotes the interaction between ER-anchored FAF2 and lysosomal mTORC1, thereby activating mTORC1 signalling and driving MASLD-driven HCC progression (132). Similarly, LINC01468 acts as a molecular scaffold that promotes CUL4A-mediated ubiquitination and degradation of the phosphatase SHIP2, thereby activating the oncogenic protein kinase B (AKT)/mTOR pathway (133). Blnc1 likewise assembles a ribonucleoprotein complex with lipogenic transcription factors to enhance lipogenic gene transcription (122) and LncSHGL recruits hnRNP A1 to enhance calmodulin translation and activate hepatic phosphatidylinositol 3-kinase (PI3K)/AKT signalling (134). circRNAs often function as miRNA sponges (or ceRNAs) sequestering miRNAs from their target mRNAs and thereby derepressing downstream oncogenes. They can also act as protein decoys or molecular scaffolds (114,135). Furthermore, some circRNAs containing internal ribosome entry sites or N6-methyladenosine

(m6A) modifications can undergo cap-independent translation to generate regulatory micropeptides, adding another layer of non-canonical protein-coding activity within the non-coding transcriptome (114). Through these mechanisms, the abundance and accessibility of signalling proteins become directly linked to the expression of specific ncRNAs, providing an additional axis through which ncRNAs influence the malignant transformation of hepatocytes.

miRNAs and MASLD. miRNAs are a class of ncRNAs, typically 21-24 nucleotides in length, that primarily regulate gene expression through post-transcriptional gene silencing. They exert their effects through partial base pairing with the 3'UTR of target mRNAs, resulting in mRNA degradation or translational repression (136).

Accumulating evidence indicates that miRNAs are intimately involved in the initiation, development and progression of MASLD, largely through the regulation of hepatic lipid metabolism and insulin sensitivity. Dysregulation of specific miRNAs has been shown to contribute to MASLD pathogenesis. For instance, increased miR-124-3p expression promotes hepatic steatosis and inflammation by suppressing Pref-1 (137), whereas miR-130b-5p exacerbates lipid accumulation and insulin resistance by targeting IGFBP2 and inhibiting the AKT signalling pathway (138). Conversely, reduced miR-338-3p expression diminishes suppression of PP4R1, impairing PP4R1/PP4 axis function and disrupting insulin signalling (139).

In addition, miR-378 and nuclear respiratory factor 1 (NRF1) form a pathogenic positive feedback loop. miR-378 inhibits NRF1-mediated fatty acid oxidation, while reduced NRF1 activity further enhances miR-378 transcription, thereby aggravating hepatic steatosis (140). The oncogenic miRNA miR-21 promotes *de novo* lipogenesis during the early stages of MASLD by suppressing the HBP1/p53 axis, relieving repression of the master lipogenic regulator SREBP-1c (141). By contrast, miR-223 protects against steatohepatitis by targeting inflammatory and oncogenic mediators, including CXCL10 and Taz (142).

lncRNAs and MASLD. lncRNAs are characterised by their lack of protein-coding capacity, and their transcriptional products are typically RNA molecules >200 nucleotides that lack functional open reading frames (143). Accumulating evidence indicates that lncRNAs serve important regulatory roles in a range of diseases, with particularly prominent involvement in the initiation and progression of MASLD. A study has shown that lncRNAs modulate signalling pathways associated with hepatic lipid metabolism, steatohepatitis, steatohepatitis-associated fibrosis and HCC, thereby contributing to MASLD pathogenesis (144).

During MASLD initiation and progression, lncRNAs play central roles in regulating lipid metabolism and inflammatory responses. A study has demonstrated that lncRNA-AK026 expression is markedly upregulated in MASLD models and may promote intracellular lipid accumulation in hepatocytes through the PPAR signalling pathway (145). GAS5 has been shown to aggravate hepatic steatosis by acting as a molecular sponge for miR-29a-3p, thereby relieving its inhibitory effect on NOTCH2 (131). In parallel, formation of the

miR-378/Nrf1 negative feedback loop further suppresses fatty acid oxidation, leading to lipid accumulation (140). As the disease progresses, the cholesterol-sensing molecule SNHG6 assembles a SNHG6-FAF2-mTOR complex, which promotes cholesterol-dependent lysosomal recruitment and activation of mTORC1. This establishes a vicious cycle that enhances lipid synthesis and signal transduction, thereby driving progression from simple steatosis to MASH (146). Notably, loss of Dicer in hepatocytes reduces miR-192-3p expression, increasing insulin-like growth factor 2 (IGF2) expression, which promotes M1 macrophage polarisation and exacerbates inflammation (147). Therapeutic approaches targeting these pathways, such as RORA agonists, can increase miR-122 expression and subsequently suppress key lipogenic enzymes, representing a potential strategy for reversing hepatic steatosis (148).

circRNAs and MASLD. circRNAs are a distinct class of single-stranded RNA molecules characterised by a covalently closed loop structure that distinguishes them from linear RNAs. This unique conformation confers remarkable stability, rendering them resistant to degradation by RNA exonucleases as they lack free 5' and 3' termini (149). Growing evidence suggests that circRNAs contribute to MASLD pathogenesis by regulating diverse biological processes, including lipid metabolism, autophagy, inflammatory responses, oxidative stress and fibrosis (150,151). A study has further demonstrated that circRNAs can regulate hepatic lipid metabolism through signalling pathways such as JAK2/STAT5 (152). RNA sequencing and bioinformatic analyses have identified 93 differentially expressed circRNAs in a mouse model of MASLD, highlighting their potential utility as cellular biomarkers (153). Consequently, circRNAs have emerged as promising blood-based biomarkers for early MASLD diagnosis.

Inflammation is a key mechanism driving progression from MASLD to MASH and is characterised by immune cell infiltration within hepatic lobules and the release of pro-inflammatory cytokines. circRNAs are involved in this process by regulating HSC activation and macrophage function. For example, circRSF1 promotes inflammatory responses (150), whereas circPSD3 exerts anti-inflammatory effects (154). However, some of these mechanistic findings come from non-MASH models, and their clinical relevance requires further validation.

4. ncRNAs and HCC

miRNAs and HCC. During the transition from MASLD to HCC, alterations in miRNA expression profiles drive hepatocarcinogenesis by promoting cell proliferation, survival and the establishment of a tumour-promoting microenvironment. One of the earliest critical events is the silencing of miR-122, the most abundant liver-specific miRNA, which occurs before malignant transformation and serves as an important molecular marker (155). Loss of miR-148a accelerates hepatocarcinogenesis by derepressing multiple target genes, including HMGCR, PGC1 α , SIRT7 and YBX1, disrupting lipid homeostasis (156). Similarly, miR-27a promotes obesity-associated HCC by suppressing the tumour suppressor BTG2, resulting in mitochondrial dysfunction and enhanced

cellular proliferation (157). In addition, miR-27a mediates the transgenerational transmission of HCC susceptibility. Maternal obesity increases miR-27a-3p expression, which represses protective genes, including ACSL1 and ALDH2, in the livers of offspring (158). Conversely, loss of miR-4310 promotes HCC growth and metastasis by releasing the inhibitory control of lipogenic enzymes FASN and SCD1, thereby providing tumour cells with substrates required for lipid biosynthesis (159).

Activation of HSCs and fibrosis development are critical precancerous events in hepatocarcinogenesis. miR-98 suppresses these processes by targeting hepatic leukaemia factor and inhibiting the HIF-1 α /TGF- β signalling axis (160). By contrast, the protective miRNA miR-223 retains its tumour-suppressive activity in HCC by repressing oncogenic mediators such as TAZ (142).

lncRNAs and HCC. In the malignant transition from MASLD to HCC, lncRNAs contribute to tumour development by modulating the tumour microenvironment and regulating oncogenic signalling pathways. Downregulation of the tumour-suppressive lncRNA FTX reduces its ability to promote M1 polarisation of Kupffer cells, thereby weakening hepatic antitumour immune surveillance (161). Concurrently, persistent activation of the miR-192-3p/IGF2 axis, resulting from hepatocyte-specific Dicer deletion, sustains the infiltration of protumorigenic M1-like macrophages (147). During tumour initiation, LINC00624 promotes hepatocarcinogenesis by disrupting the HDAC6/TRIM28/ZNF354C transcriptional repressor complex, activating neighbouring oncogenes, including CHD1L and BCL9 (162).

These findings are consistent with mechanisms described in previous reviews, which indicate that lncRNAs exert their functions through diverse modes of action, including serving as molecular scaffolds, miRNA sponges and epigenetic regulators (163). Among these, LINC01468 enhances *de novo* lipogenesis and tumour proliferation by recruiting CUL4A to promote the ubiquitin-mediated degradation of SHIP2, thereby relieving suppression of the PI3K/AKT/mTOR signalling pathway (133).

circRNAs and HCC. The biological functions of circRNAs in HCC have been extensively characterised over the past decade. Accumulating evidence indicates that circRNAs primarily act as miRNA sponges, representing a central mechanism through which they exert both tumour-suppressive and oncogenic effects during HCC development. Tumour-suppressive circRNAs, including circLIFR and circ_0005986, inhibit tumour progression by sequestering oncogenic miRNAs and consequently suppressing key signalling pathways, such as β -catenin and Notch (164,165). By contrast, oncogenic circRNAs, including circTMEM45A and hsa_circRNA_104348, promote HCC progression by releasing miRNA target genes from repression and aberrantly activating protumorigenic pathways, including IGF2 and Wnt/ β -catenin signalling (166,167).

circGPR137B is a tumour-suppressive circRNA that acts as a sponge for miR-4739, thereby attenuating its inhibitory effect on the tumour suppressor fat mass and obesity-associated protein (FTO). Moreover, FTO enhances circGPR137B stability through m6A demethylation, forming a positive

feedback loop that collectively suppresses HCC initiation and metastasis (168). These mechanistic findings highlight the considerable potential of circRNAs as prognostic biomarkers and therapeutic targets in HCC.

5. ncRNAs and the progression of MASLD-driven HCC

miRNAs and the progression of MASLD-driven HCC. MASLD has emerged as a global health challenge, with disease progression spanning a continuum from simple hepatic steatosis to MASH, fibrosis, cirrhosis and ultimately HCC. This progression is driven by complex interactions among metabolic stress, chronic inflammation, oxidative injury and genetic alterations. Although aberrant ncRNA expression has been extensively documented in both MASLD and HCC, the specific regulatory mechanisms underlying the transition from MASLD to HCC remain incompletely elucidated.

Upregulation of pro-steatotic miRNAs is a major contributor to early-stage simple steatosis. For example, miR-34a impairs fatty acid oxidation by suppressing PPAR α (169), whereas miR-21 disrupts lipid homeostasis by targeting PPAR α (170). Similarly, miR-22 promotes hepatic steatosis by directly targeting SIRT1 and suppressing PPAR α expression, thereby driving lipid accumulation and amplifying TNF- α and IL-6 production (171). Evidence has shown that NF- κ B induces miR-155-5p expression, which suppresses STC1 and leads to mitochondrial dysfunction in hepatocytes, thereby accelerating MASLD progression (172). By contrast, downregulation of protective miRNAs such as miR-192-5p promotes lipid accumulation by derepressing its target gene, SCD1 (173).

Progression to MASH is characterised by intensified inflammatory responses. Under lipotoxic conditions, hepatocyte-derived extracellular vesicles deliver miR-9-5p to macrophages, promoting a pro-inflammatory M1 phenotype by inhibiting transglutaminase 2 (TGM2) and amplifying IL-1 β , IL-6 and TNF- α production, thereby exacerbating hepatic inflammation (174). miR-21 further amplifies inflammatory signalling through repression of SMAD7 and PDCD4 (170). By contrast, miR-146a and miR-690 exert anti-inflammatory effects by promoting M2 polarization, with miR-146a targeting IRAK1/TRAF6 and miR-690 targeting NADK, thereby attenuating inflammation (175). Furthermore, loss of miR-122 increases inflammatory cytokine expression, including IL-6 and TNF- α , accelerating MASH progression (176). Notably, inhibition of miR-375 exerts protective effects in MASLD through AdipoR2-dependent regulation of adipokines and suppression of inflammatory cytokine production (177). Of particular interest, genetic deletion of miR-33 prevents progression from MASH to HCC by promoting favourable metabolic reprogramming, highlighting its therapeutic potential (178).

HSC activation is a pivotal event in hepatic fibrogenesis. Hepatic miR-21 is upregulated in NASH/MASLD and contributes to hepatocellular injury, inflammation and fibrogenesis, chiefly by repressing PPAR α in inflammatory and biliary cells and by targeting phosphatase and tensin homolog (PTEN) (170); sustained upregulation reinforces a lipotoxic and profibrotic programme that can progress toward MASH-related HCC (179,180). Likewise, increased miR-188-5p expression exacerbates fibrosis by activating the PTEN/PI3K/AKT signalling pathway (181). Conversely,

protective miRNAs such as miR-29a exert anti-fibrotic effects by directly targeting fibrogenic mediators such as COL1A1 and by dampening TGF- β /SMAD3-driven hepatic stellate cell activation (182). Downregulation of miR-372-3p in patients with MASH promotes fibrosis through loss of repression of AEBP1, a critical driver of HSC activation (183).

The final transition to HCC is accompanied by marked miRNA dysregulation. Oncogenic miRNAs, including miR-182-5p, promote tumour development by inhibiting tumour suppressors such as CYLD and FOXO1 (184). Conversely, loss of tumour-suppressive miRNA activity plays a critical role in hepatocarcinogenesis. Silencing miR-122 is recognised as an early event in malignant transformation (155), whereas loss of miR-223 accelerates progression from MASH to HCC by derepressing inflammatory and oncogenic pathways (142). Other miRNAs, including miR-132, have been associated with disease severity by simultaneously promoting steatosis and hyperlipidaemia through multiple downstream targets (185).

In summary, miRNAs form an intricate regulatory network throughout the MASLD-MASH-HCC disease continuum and represent promising biomarkers for disease stratification, as well as attractive therapeutic targets. A preclinical study demonstrating the efficacy of miR-22 inhibition (186) and miR-29a supplementation strongly support the development of miRNA-based therapeutic strategies aimed at halting or reversing disease progression. Furthermore, recent single-cell analyses have characterised the distinct tumour microenvironment of MASLD-driven HCC and identified FABP4 as a prognostic biomarker (187). These findings provide valuable insights into prognostic stratification and targeted therapeutic development for this increasingly prevalent form of liver cancer.

lncRNAs and the progression of MASLD-driven HCC. Once regarded as ‘transcriptional noise’, lncRNAs are now recognised as pivotal epigenetic regulators in the pathogenesis of MASLD and its progression to HCC. These RNAs coordinate gene expression at both the transcriptional and translational levels, thereby driving key pathological processes, including metabolic dysregulation, inflammation, fibrosis and malignant transformation.

During the initiation of hepatic steatosis, pro-steatotic lncRNAs promote aberrant *de novo* lipogenesis. For example, SRA facilitates lipid accumulation by modulating the p38/JNK phosphorylation balance and directly activating the insulin receptor gene (123,124). Similarly, Blnc1 forms a ribonucleo-protein complex with transcription factors to enhance the transcription of lipogenic genes through the LXR-SREBP1c pathway, and its liver-specific deletion ameliorates steatosis and insulin resistance in obese mice (122). The lncRNA Gm15622, which is upregulated in obesity, functions as a ceRNA by sequestering miR-742-3p, thereby derepressing its target SREBP-1c and accelerating lipogenesis. Notably, metformin alleviates steatosis, in part through suppression of Gm15622 (188). Furthermore, NEAT1 promotes hepatocellular lipid accumulation by sponging miR-146a-5p and upregulating ROCK1 expression (189). MALAT1 has also been reported to enhance hepatic lipid production and drive MASLD progression by inhibiting miR-206, thereby increasing ARNT expression and activating the PPAR α /CD36

pathway (190). Conversely, NEAT1 downregulation inhibits mTOR/S6K1 signalling, effectively reducing hepatic lipid deposition, inflammation and injury, highlighting its potential as a therapeutic target in MASLD (191). NEAT1 also binds miR-129-5p, regulates PEG3 expression and contributes to HSC activation in MASH (192). By contrast, the protective lncRNA Mirt2 is downregulated in MASLD. Its upregulation attenuates steatosis by sponging miR-34a-5p, resulting in USP10 upregulation and subsequent inhibition of the master lipogenic transcription factor SREBP-1 (193).

Chronic inflammation and HSC activation drive progression to steatohepatitis and fibrosis, and specific lncRNAs influence both. The protective lncRNA LncSHGL is downregulated during this stage. Restoration of LncSHGL recruits hnRNPA1, enhancing calmodulin translation and activating the PI3K/AKT pathway. This activation suppresses gluconeogenesis while inhibiting the mTOR/SREBP-1 pathway, thereby reducing lipogenesis (134). The role of GAS5 appears to be context dependent; it is highly expressed in MASLD, where it sponges miR-29a-3p, upregulates NOTCH2 expression and promotes disease progression (131). In experimental fibrosis models, however, GAS5 upregulation suppresses HSC activation by sponging miR-23a and restoring PTEN expression (194).

The transition to HCC involves impaired antitumour surveillance and activation of oncogenic pathways, processes strongly influenced by lncRNAs. H19 is highly expressed during liver development and is re-induced in NAFLD-related steatosis. It also enhances hepatic lipogenesis through distinct mechanisms: The H19/PTBP1/SREBP1 feed-forward loop stabilizes SREBP1c and promotes its nuclear translocation (125), whereas H19 also activates the MLXIPL transcriptional network and the mTORC1 signalling axis to drive lipid accumulation (126). In addition, H19 acts as a ceRNA for miR-130a, increasing PPAR γ expression (195). The inflammatory lncRNA lncTNF, which is upregulated in MASLD, exacerbates chronic inflammation through NF- κ B activation (196). Remodelling of the immune microenvironment is also critical. SNHG20 promotes the polarisation of Kupffer cells from the antitumour M1 phenotype to the pro-tumour M2 phenotype through STAT6 activation (197). By contrast, FTX functions as a tumour suppressor and impedes MASLD-driven HCC progression. This lncRNA acts as an immunometabolic checkpoint by regulating the balance between M1 and M2 Kupffer-cell polarisation, suppressing the protumorigenic M2 phenotype, reducing inflammation and inhibiting carcinogenesis (161). Moreover, LINC01468 functions as a molecular scaffold that promotes ubiquitination and degradation of the phosphatase SHIP2, thereby activating the oncogenic AKT/mTOR pathway and driving NAFLD-HCC tumorigenesis (133). Recently, lnc-OXAR was identified as a key mediator of oxaliplatin resistance in MASH-HCC. Regulated by the m6A-WTAP/IGF2BP2 axis, this lncRNA enhances DNA damage repair through Ku70/CSTA and represents a promising therapeutic target (198).

In summary, lncRNAs form a dynamic, interconnected regulatory network that orchestrates each stage of the MASLD-driven HCC continuum. A comprehensive understanding of this network not only provides insight into the underlying pathogenic mechanisms but also identifies

promising stage-specific diagnostic biomarkers and therapeutic targets.

circRNAs and the progression of MASLD-driven HCC. In the initiation and progression of hepatic steatosis, circRNAs primarily regulate early-stage disease phenotypes by modulating lipid metabolism and oxidative stress homeostasis. circRNA_0046366 alleviates hepatic steatosis by sponging miR-34a and enhancing PPAR α -mediated fatty acid β -oxidation (130). Conversely, reduced circRNA_0046367 expression weakens its protective effect against hepatocyte lipid peroxidation, thereby promoting lipid accumulation (199). Gain-of-function experiments show that nanodrug delivery of circRNA_0001805 ameliorates hepatic steatosis in mouse models by regulating the miR-106a-5p/miR-320a and ABCA1/CPT1 axes (200). Notably, the functional peptide circ-SLC9A6-126aa, translated from circ-SLC9A6, acts as a key driver of the steatosis/MASLD stage by activating CD36 transcription in an H4K16ac-dependent manner, thereby directly promoting hepatic lipid uptake and deposition (127).

During MASH development, inflammatory responses and cellular stress are the predominant pathogenic events, and circRNAs help regulate both the immune microenvironment and cellular homeostasis. Downregulation of CiR-EIS reduces its ability to sponge miR-548m, suppressing IGF1 expression and impairing macrophage polarisation toward an anti-inflammatory M2-like phenotype, thereby exacerbating MASH-associated inflammation (201). Through a non-canonical mechanism, circPI4KB facilitates extracellular export of miR-122, reducing its intracellular abundance and indirectly aggravating hepatic lipid accumulation and injury within the inflammatory microenvironment (202). Furthermore, lipids suppress circRNA SCAR expression through the ER stress/PGC-1 α axis; its downregulation results in mitochondrial dysfunction and accumulation of mitochondrial ROS, directly promoting fibroblast-mediated metaflammation and establishing a critical link between metabolic stress and inflammation (10).

As disease progresses to fibrosis, HSC activation becomes a central event in fibrogenesis. In a methionine and choline-deficient-diet-induced mouse NASH model, circRNA_29981 is markedly upregulated and bioinformatic analysis suggests it may regulate HSC activation by sequestering miRNAs, including miR-181b-5p, indicating a potential role in fibrosis. However, this proposed ceRNA mechanism remains to be experimentally validated (203).

In MASH-associated hepatocarcinogenesis, circRNAs function as either oncogenic or tumour-suppressive regulators. circSMEK1 is significantly downregulated in MASH-HCC, and disruption of its tumour-suppressive activity through the hnRNPK-IGF2-AKT signalling axis markedly promotes hepatocarcinogenesis. Serum circSMEK1 levels have demonstrated diagnostic potential, while therapeutic strategies targeting this pathway may provide new opportunities for HCC prevention and treatment (204).

ncRNA-metabolism interplay in MASLD-driven HCC progression. MASLD is fundamentally a metabolic disorder, and metabolic dysregulation represents a defining feature of the progression from MASLD to HCC. As discussed in

previous sections, ncRNAs actively regulate lipid metabolism, glucose metabolism, inflammatory responses and fibrogenesis throughout this disease continuum. Notably, this interaction is bidirectional, not unidirectional. Metabolic intermediates and nutrient availability can reciprocally influence ncRNA expression and function, establishing self-perpetuating feedback loops that sustain metabolic dysfunction. Emerging evidence shows a complex interplay between metabolic reprogramming and epigenetic regulation, including ncRNA-mediated mechanisms, which collectively drive MASLD-driven HCC progression (205).

Within this regulatory framework, lipid metabolism occupies a central role. During hepatic steatosis development, miR-34a and miR-21 target and suppress PPAR α , a key transcription factor that promotes fatty acid β -oxidation, thereby reducing fatty acid catabolism (169,170). Simultaneously, miR-22 upregulation suppresses FGF21 and FGFR1, reduces AMP-activated protein kinase (AMPK; and ERK1/2) activation, and thereby promotes hepatic lipogenesis and fat accumulation (steatosis) (206). Together, these miRNAs cooperate to drive hepatic lipid accumulation. By contrast, circRNA_0046366 functions as a molecular sponge for miR-34a, relieving PPAR α suppression and enhancing PPAR α -mediated fatty acid β -oxidation, thereby attenuating hepatic steatosis (130). Furthermore, MALAT1 sponges miR-206, increasing ARNT expression and activating the PPAR α /CD36 pathway, which promotes lipogenesis (190). Collectively, these findings indicate that distinct classes of ncRNAs converge on common metabolic regulators through mechanisms including post-transcriptional repression, transcriptional co-activation and molecular sponging, thereby forming a multilayered regulatory network.

In the MASLD liver, insulin resistance and persistent hyperglycaemia further reshape the ncRNA expression landscape. The aforementioned miR-22-mediated suppression of AMPK not only enhances lipogenesis but also aggravates insulin resistance and glucose dysregulation (171,206-208). As disease progresses toward HCC, oncogenic miR-182-5p enhances glucose uptake and lactate production by targeting Cyld and Foxo1 (184), whereas lncRNA H19 promotes glycolysis through mTORC1 signalling (125,126). This metabolic reprogramming not only supports rapid tumour growth but also creates an acidic, immunosuppressive microenvironment, reinforcing metabolic-immune crosstalk.

Notably, the relationship between ncRNAs and metabolism is reciprocal. As aforementioned, lipotoxic stress induces hepatocytes to release extracellular vesicles containing miR-9-5p, which drive macrophage polarisation toward a pro-inflammatory M1 phenotype by inhibiting TGM2 and amplifying IL-1 β , IL-6 and TNF- α production (174). Cholesterol overload activates the SNHG6-FAF2-mTOR complex, establishing a feedforward loop that further amplifies lipogenic signalling (146). In addition, metabolite-responsive transcription factors, including PPAR, LXR and SREBP, can directly regulate ncRNA transcription through promoter binding, thereby linking nutrient availability to ncRNA expression (209-211). Metabolic cofactors such as NAD⁺/NADH and acetyl-CoA also modulate epigenetic enzyme activity, adding another layer of metabolic-epigenetic-ncRNA interaction. For example, the m⁶A demethylase FTO stabilises circGPR137B, establishing a

positive feedback loop that suppresses HCC progression (168). Collectively, these findings demonstrate that ncRNAs are dynamically regulated by the metabolic environment that they simultaneously shape.

From a translational perspective, the ncRNA-metabolism axis provides several therapeutically actionable targets with considerable clinical potential. Metformin, a widely used first-line antidiabetic agent, partially alleviates MASLD by suppressing the Gm15622/miR-742-3p/SREBP-1c axis (188), illustrating that approved metabolic therapies can exert part of their therapeutic effect through ncRNA modulation. A recent review systematically summarised multiple clinical studies and highlighted the therapeutic potential of targeting the ncRNA-metabolism axis (212). AZD4076 (RG-125), a GalNAc-conjugated anti-miR-103/107 oligonucleotide designed to relieve caveolin-1 suppression and improve insulin sensitivity, has undergone Phase I evaluation. Trial NCT02612662 assessed its safety and pharmacokinetic profile in healthy volunteers, while NCT02826525 completed Phase I evaluation in patients with NAFLD and type 2 diabetes; however, subsequent development was discontinued. Although the planned enrolment of this study was 51, only 14 subjects were ultimately enrolled, and development of RG-125 was halted in Phase II in 2017 after serious adverse events were reported for one of the other miRNA-targeting agents under clinical development by the company alliance behind RG-125; the discontinuation therefore reflected safety findings related to a different programme within the alliance rather than any reported failure of AZD4076 itself (212). RES-010, a locked nucleic acid-modified anti-miRNA oligonucleotide targeting miR-22-5p, has been developed to restore lipid metabolic regulation and promote white-to-brown adipose tissue conversion for the treatment of MASLD/MASH, and entered Phase I clinical evaluation in 2024 (EudraCT No.2024-514871-17-00). In addition, MRX34, a liposome-encapsulated miR-34a mimic (NCT01829971), was tested in completed a Phase I study on patients with advanced solid tumours, including HCC. Although the trial was terminated due to immune-related adverse events, it provided the first clinical proof of concept for miRNA mimic therapy and generated valuable insights for developing next-generation ncRNA delivery platforms. Nevertheless, efficient delivery, off-target effects and the context-dependent nature of ncRNA function remain major challenges, and each is exemplified by specific clinical experience: Delivery-related toxicity of MRX34 was observed, whose liposomal vehicle was implicated in the immune-related serious adverse events that terminated the trial; however, a distinct delivery trade-off is seen with hepatocyte-selective GalNAc conjugation, which improves hepatocyte targeting but limits access to Kupffer cells and hepatic stellate cells, an issue not addressed by the MRX34 experience, where the primary problem was vehicle-related toxicity rather than cell-type selectivity; sequence-dependent off-target regulation is exemplified by the miR-103/107 family, which regulates additional metabolic transcripts beyond caveolin-1 (212); and context-dependent activity is exemplified by GAS5, which promotes MASLD progression by sponging miR-29a-3p yet restrains fibrosis by sponging miR-23a (131,194), and by miR-34a, which drives hepatocyte steatosis yet is exploited as a tumour-suppressive mimic in HCC, whereby the same molecule may exert distinct

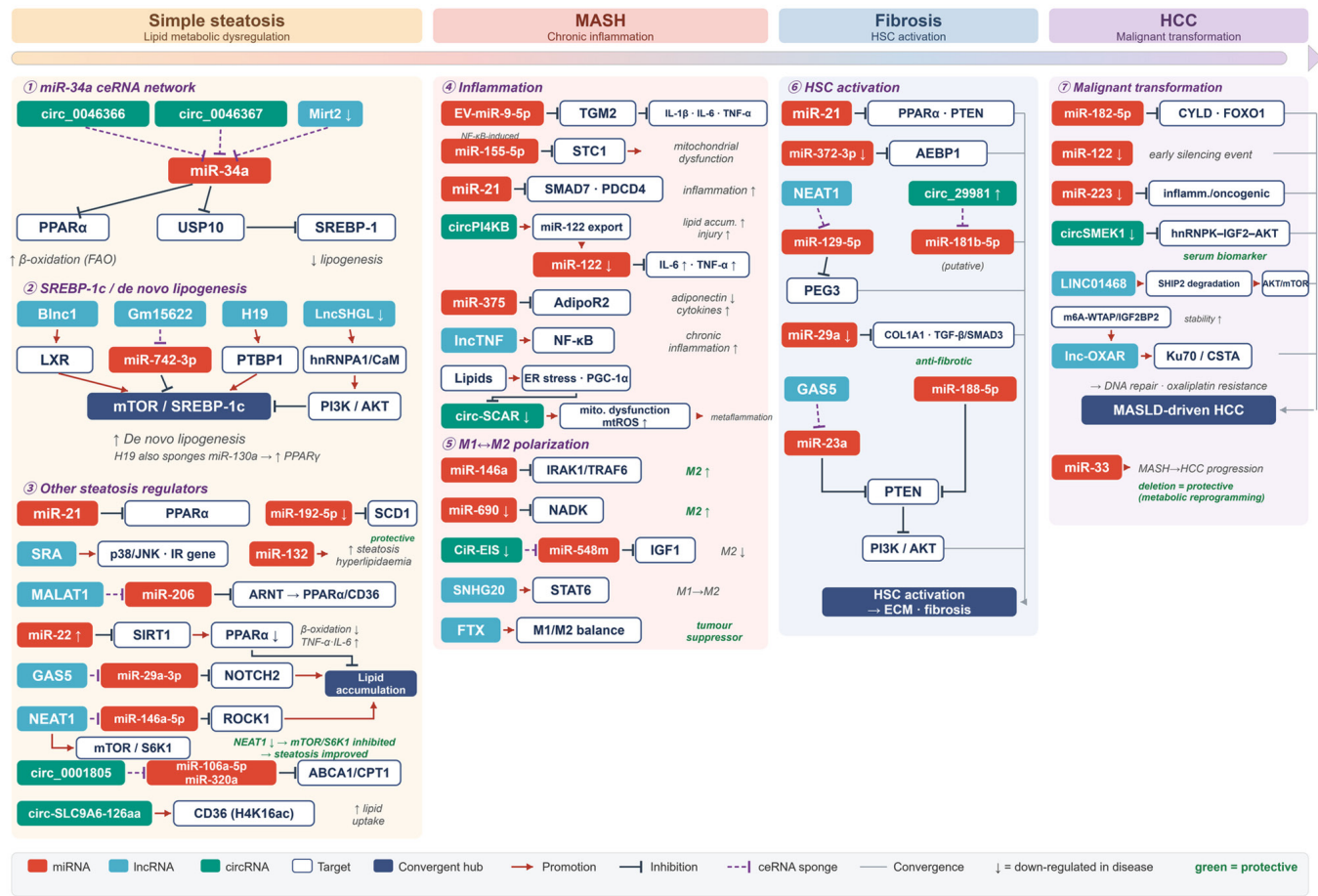


Figure 7. Key regulatory network of ncRNAs during the progression from MASLD to HCC. The diagram is organised into four disease stages (simple steatosis, MASH, fibrosis and HCC) and illustrates how miRNAs (red), lncRNAs (blue) and circRNAs (green), together with their target molecules (white) and the convergent signalling hubs (dark blue), play crucial roles in this disease process, either promoting or inhibiting it through complex interactions. Regulatory mechanisms shared by different ncRNA classes are merged into convergent hubs, including the miR-34a ceRNA axis, the SREBP-1c lipogenic hub, the lipid-accumulation node, the PTEN/PI3K/AKT node, the M1/M2 macrophage-polarisation hub and the HSC-activation hub, thereby highlighting the convergent regulatory networks underlying MASLD-driven HCC progression. Among them, certain lncRNAs and circRNAs can function as ceRNAs that modulate miRNA activity via a sponge mechanism (purple dashed lines), thereby influencing downstream target genes and signalling pathways and, collectively, driving the evolution of disease phenotypes. Red arrows indicate promotion/activation, dark T-bars indicate inhibition, grey lines denote convergence onto stage-specific hubs, ↓ denotes downregulation in disease, and green labels mark protective factors. ncRNAs, non-coding RNAs; MASLD, metabolic dysfunction-associated steatotic liver disease; HCC, hepatocellular carcinoma; miRNAs, microRNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; ceRNAs, competing endogenous RNAs; MASH, metabolic dysfunction-associated steatohepatitis; HSC, hepatic stellate cell. Created with figdraw.com.

or even opposing effects at different disease stages (213,214). These limitations highlight the need for precisely designed ncRNA-targeted interventions tailored to both disease stage and cellular context.

In summary, this section highlights the regulatory roles of the three major classes of ncRNAs, namely miRNAs, lncRNAs and circRNAs, in the progression from MASLD to HCC (Fig. 7 and Table SI). These ncRNAs coordinate a complex regulatory network by modulating key pathological processes, including lipid metabolism, inflammatory responses, fibrogenesis and malignant transformation. At a broader level, the interplay between ncRNAs and metabolic reprogramming constitutes a critical driver of MASLD-driven HCC progression. Consequently, these ncRNAs, together with the signalling pathways they regulate, represent promising biomarkers for disease-stage assessment and attractive therapeutic targets. Ultimately, targeting this regulatory axis represents a promising avenue for developing precision strategies for the prevention, diagnosis and treatment of MASLD-driven HCC.

6. Conclusions and future perspectives

The progression from MASLD to HCC is a complex, multifactorial pathological process driven by the interplay of metabolic dysregulation, chronic inflammation, oxidative stress, immune dysfunction and gut microbiota imbalance. The present review systematically highlights the central regulatory roles of ncRNAs, including miRNAs, lncRNAs and circRNAs, across this disease continuum. By orchestrating the fine-tuned regulation of key signalling pathways, particularly NF-κB, JAK/STAT and PI3K/AKT/mTOR, these ncRNAs exert notable effects on lipid metabolism, inflammatory responses, fibrogenesis and hepatocellular malignant transformation, thereby promoting disease progression across the entire spectrum from simple steatosis to MASH, liver fibrosis/cirrhosis and ultimately HCC.

Mechanistically, MASLD-driven HCC progression is driven by multiple interconnected processes, including chronic inflammation, oxidative stress, immune dysregulation, gut

microbiota imbalance, lipotoxicity and glucotoxicity. ncRNAs play critical regulatory roles at different stages of disease development through diverse mechanisms, including molecular sponging, scaffold formation and, in some cases, the encoding of functional micropeptides that enable precise control of cellular processes. Despite substantial progress, most studies have focused on individual ncRNAs, while interactions among different classes of ncRNAs remain poorly understood. Future investigations should therefore move beyond a single-molecule perspective and adopt a network-based approach to elucidate potential synergistic, additive or antagonistic relationships among ncRNAs and define their integrated downstream signalling networks.

The close association between ncRNA expression profiles and disease severity across the MASLD-driven HCC continuum highlights their considerable translational potential. Future advances are likely to focus on two major directions. First, developing non-invasive biomarkers for diagnosis and dynamic disease monitoring is a key priority. Several ncRNAs, including circulating miR-122 and miR-34a, have demonstrated strong associations with disease progression and may be incorporated into biomarker panels following validation in large-scale clinical cohorts. Such panels could provide non-invasive tools for early detection, risk stratification, disease monitoring and therapeutic response assessment, overcoming limitations of current diagnostic approaches. Second, precision therapeutic strategies targeting ncRNAs represent a promising avenue for disease intervention. Silencing pathogenic ncRNAs, such as miR-21 and miR-155, with chemically modified inhibitors (including antagomirs) or restoring the activity of protective ncRNAs, such as miR-122, through synthetic mimics, could modulate disease progression at the molecular level.

Recent advances in oligonucleotide engineering, delivery technologies and targeted RNA therapeutics have further accelerated the clinical development of ncRNA-based interventions. Nevertheless, several substantial challenges remain, including efficient and tissue-specific delivery, long-term safety, off-target effects and the context-dependent functions of ncRNAs across different disease stages and cellular environments. Addressing these limitations will be essential for successful clinical translation.

In conclusion, ncRNAs are not merely passive biomarkers but active regulators of the molecular events underlying MASLD-driven HCC progression. Their extensive involvement in metabolic regulation, inflammation, fibrosis and hepatocarcinogenesis places them at the centre of disease pathogenesis. A more comprehensive understanding of ncRNA regulatory networks will not only provide deeper insight into the mechanisms driving MASLD-associated hepatocarcinogenesis but also facilitate the development of innovative diagnostic, prognostic and therapeutic strategies. Ultimately, integration of ncRNA-based approaches with existing clinical management paradigms may enable more precise and effective prevention and treatment of MASLD-driven HCC.

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Authors' contributions

HW conceived the topic of review. WZ, CA, LX, HW, YW and JZ wrote, reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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