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Review

Breaking Down MASLD: Insights into Its Complex Pathophysiology

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Article information

Received date: 28/02/2025; **Accepted date:** 25/04/2025; **Published date:** 24/05/2025

ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease globally, causing increasing morbidity and mortality. Over the past two decades, our understanding of the disease's pathophysiology and genetics has significantly improved.[1] In 2020, "metabolic dysfunction-associated fatty liver disease" (MAFLD) was proposed, and "metabolic dysfunction-associated steatotic liver disease" (MASLD) and "metabolic dysfunction-associated steatohepatitis" (MASH) were proposed in 2023. These changes aim to introduce a new framework for researchers, practitioners, and patients, allowing for the classification of various liver disorders with abnormal fat accumulation within the steatotic liver disease (SLD) construct.[2]

The term "metabolic dysfunction-associated fatty liver disease" (MAFLD) and "metabolic dysfunction-associated steatotic liver disease" (MASLD) has evolved due to increased understanding of the link between local and systemic pathogenic pathways.[2]

Hepatic steatosis, commonly known as fatty liver, is becoming a growing health concern worldwide, affecting people of all ages. Beyond its potential to progress to severe liver conditions like inflammation, fibrosis, cirrhosis, or even liver cancer, it has reported to heighten the risk of developing cardiovascular diseases, metabolic disorders, and certain types of cancer.[2]

Managing MASLD is challenging due to its complex nature, influenced by a combination of metabolic, genetic, and environmental factors. This complexity makes it difficult to develop effective treatment and prevention strategies that work for everyone.[3] With its rising prevalence, understanding how the disease develops has become more urgent.[4]

Materials and Method: Review and extracting data from Articles which have published data related to pathophysiology of MASLD.

Results and Conclusion: Several studies have found that MASLD progression is driven by complex metabolic and molecular mechanisms, including impaired lipid metabolism, mitochondrial dysfunction, and inflammation. Key contributors include the inhibition of apolipoprotein A5 (apoA5) secretion, elevated selenoprotein P (SeP) levels, and hypoxia-induced overexpression of hypoxia-inducible factor 2 alpha (HIF-2α), which suppresses peroxisome proliferator-activated receptor alpha (PPARα) expression and worsens lipid accumulation. Disruption of the fibronectin type III domain-containing protein 5 (FNDC5)/AMP-activated protein kinase alpha (AMPKα) pathway by microRNA-665-3p further promotes oxidative stress and inflammation. Emerging therapeutic strategies, such as targeting miR-665–3p, SeP inhibition, and hypoxia alleviation, hold promise for restoring metabolic balance and managing MASLD. Future research should focus on translating these insights into effective clinical applications.

Keywords: MASLD, risk factors, insulin resistance, inflammation, multiple-hit hypothesis

Introduction

Aim: This review aimed to gain more understanding about the pathophysiology of MASLD.

Methods: Several articles related to topic of discussion which pathophysiology of MASLD were reviewed and data was extracted from them.

Results: The progression of MASLD is influenced by complex metabolic and molecular mechanisms. Key findings highlight the inhibition of apolipoprotein A5 (apoA5) secretion, leading to triglyceride accumulation and hepatic steatosis. Elevated levels of selenoprotein P (SeP) impair lipid metabolism, worsening the disease. Hypoxia-induced overexpression of hypoxia-inducible factor-2α (HIF-2α) suppresses PPARα expression, exacerbating mitochondrial dysfunction and lipid accumulation. MicroRNA-665–3p disrupts the FNDC5/AMPKα pathway, promoting oxidative stress and inflammation. Targeting these pathways, such as through miR-665–3p antagonism, SeP inhibition, and hypoxia alleviation, presents potential therapeutic avenues for MASLD management.

Discussion

Global prevalence and increasing health burden

MASLD, the most prevalent chronic liver disease worldwide, is associated with several risk factors. A BMI greater than 25 is a key risk factor, with an estimated global prevalence of 30.05%. Among overweight and obese patients who underwent liver biopsy, the prevalence of MASLD was 69.99% and 75.25% respectively. Approximately one out of five overweight or obese MASLD patients had clinically significant fibrosis. Advanced fibrosis was 6.65% and 6.68% in both groups.[5]

Recent studies have shown that lean and normal-weight healthy individuals are not even free of risk of MASLD. Visceral adiposity is more strongly associated with cardiometabolic health risk than BMI. Insulin resistance (IR) and diabetes mellitus (DM) are other important risk factors for MASLD, with a bidirectional relationship between IR and DM. All types of diabetes increase the risk of MASLD. The prevalence of MASLD is highest (55% to 76%) in patients with DM type II and lowest in patients with ketone-prone diabetics and MODY.[5]

Both obesity and DM manifest with dyslipidemia, which is strongly tied to MASLD. The prevalence of dyslipidemia ranges from 20% to 80%, depending on the presence of risk factors. Primary hyperlipidemia, either familial combined hyperlipidemia or familial hypertriglyceridemia, is associated with MASLD independent of other risk factors.[5]

The Multifaceted Nature of MASLD

MASLD is a complex condition influenced by a variety of factors, resulting in diverse clinical and histopathological features. Its progression varies significantly between individuals, driven by multiple mechanisms such as increased uptake of fatty acids from adipose tissue, heightened fat production in the liver (de novo lipogenesis), reduced triglyceride excretion, and impaired fat breakdown through mitochondrial or peroxisomal pathways.[5]

These mechanisms often result from a combination of risk factors, which can be categorized into individual characteristics, metabolic health, and genetic or epigenetic influences.[5] Individual factors such as age, gender, ethnicity, diet, physical activity, alcohol consumption, and gut microbiota composition all contribute to disease development.[5] Metabolic factors, including visceral obesity, diabetes, dyslipidemia, and hypertension, play a major role.[5]

Changes in the gut microbiome and its metabolic byproducts contribute to the progression of MASLD and related hepatocellular carcinoma. Patients with MASLD commonly display an altered Firmicutes-to-Bacteroidetes ratio, which is associated with liver fat buildup and obesity, reflecting microbial imbalance.[7]

Genetic factors, though less well understood, also influence MASLD. Variants such as Patatin-Like Phospholipase Domain-Containing Protein 3 (PNPLA3) and Transmembrane 6 Superfamily Member 2 (TM6SF2) are associated with impaired very low density lipoprotein (VLDL) excretion and the development of MASLD, though their precise impact remains unclear. Like other genetic conditions such as hemochromatosis, these variants have low penetrance, meaning carrying them does not always lead to severe disease.[5]

MASLD often occurs alongside metabolic syndrome and conditions like obesity, insulin resistance, hypertension, and elevated triglyceride levels. Excess fat buildup in the liver can trigger harmful processes such as cellular stress and organ

dysfunction, progressing to MASH. Impaired lipid metabolism, characterized by triglyceride accumulation in liver cells, is a defining feature.[4]

Importantly, MASLD can develop in individuals regardless of weight. However, visceral fat is strongly linked to higher risks of cirrhosis, liver cancer, and cardiovascular disease. A bidirectional relationship exists between MASLD and diabetes, complicating disease management. Interestingly, not all MASLD patients develop atherogenic dyslipidemia or face elevated cardiovascular risks, reflecting the complex interplay of metabolic factors.[5]

Dietary habits and lifestyle choices significantly influence MASLD by altering the gut microbiota, which affects biochemical processes that drive fat accumulation, inflammation, fibrosis, and even cancer. Given its complex nature and varied progression among individuals, understanding these contributing factors is essential for developing effective treatments.[5]

Core Pathways Leading to MASLD

Recent studies have identified various metabolism-related signaling pathways involved in the onset and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). While the exact mechanisms remain unclear, some key pathways have been highlighted.[6]

A. JNK Signaling Pathway:

A high-fat diet triggers an increase in c-Jun N-terminal kinase (JNK) 1 activity in liver cells, leading to elevated phosphorylation of insulin receptor substrate 1 (p-IRS-1Ser307). This, in turn, reduces the phosphorylation of protein kinase B (p-PKBSer473), impairing insulin signaling and contributing to insulin resistance (IR), a key factor in MASLD development.[6]

Additional stimuli, such as tumor necrosis factor-alpha (TNF-α), free fatty acids (FFAs), and oxidative stress, further activate the JNK pathway, worsening insulin resistance and promoting MASLD progression. Targeting the JNK signaling pathway, counteracting the effects of TNF-α and FFAs, or alleviating oxidative stress offers potential therapeutic approaches for preventing and managing MASLD.[6]

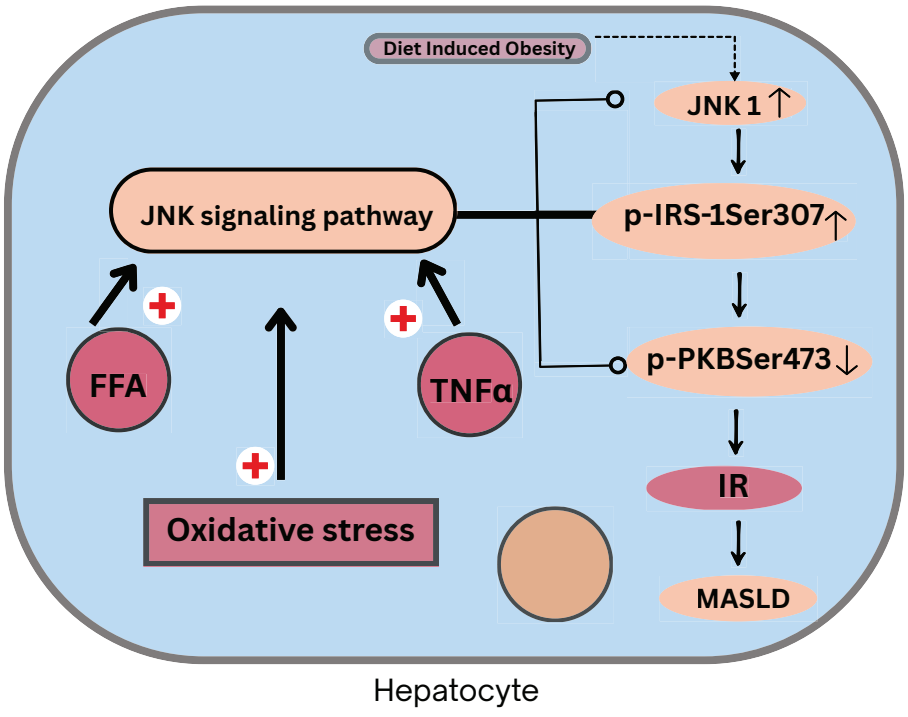

Fig 1. JNK Signaling Pathway.[6]

B. MPST/H_2S Pathway:

3-Mercaptopyruvate sulfurtransferase (MPST) is an enzyme that generates hydrogen sulfide (H_2S) from 3-thiopyruvate without the need for pyridoxal phosphate (PLP). H_2S, a gas with a distinctive rotten egg odor, is known for its protective role against liver injury caused by ischemia-reperfusion and hepatotoxins such as carbon tetrachloride (CCl_4). Within the liver, cystathionine γ-lyase (CSE) serves as the primary enzyme responsible for converting cysteine into H_2S, making it a key source of hepatic H_2S.[6]

High-fat diets (HFD) or exposure to free fatty acids (FFAs) significantly upregulate MPST expression in liver cells. MPST directly interacts with and inhibits CSE, leading to a decrease in H_2S production. This feedback loop, where MPST suppresses CSE activity, regulates the overall H_2S metabolic balance and contributes to liver fat accumulation. The activation of the sterol regulatory element-binding protein 1c (SREBP-1c) pathway, increased phosphorylation of JNK, and promotion of oxidative stress are key mechanisms involved in this process.[6]

MPST Pathway: MPST regulates H_2S production both directly and indirectly by modulating CSE activity. When MPST is inhibited, either through shRNA-mediated knockdown or heterozygous deletion, there is an increase in H_2S production and a reduction in hepatic steatosis in HFD-fed mice. The inhibitory effect of MPST on CSE occurs through direct protein–protein interactions, maintaining metabolic homeostasis of H_2S in the liver.[8]

Hydrogen sulfide (H_2S) influences liver fat accumulation through various mechanisms:

- **Regulation of Lipid Metabolic Enzymes:** Exogenous administration of H2S has been shown to reduce hepatic lipid accumulation in methionine/choline-deficient (MCD) diet-fed rats. This effect is mediated through modulation of lipid metabolism-related genes, such as peroxisome proliferator-activated receptor alpha (PPARα) and SREBP-1c.[9,10,11]
- **Activation of Autophagic Pathways:** H2S donors, like sodium hydrosulfide (NaHS), activate autophagy through the AMPK-mTOR signaling pathway, which in turn reduces serum triglyceride levels and alleviates nonalcoholic fatty liver disease (MASLD) in high-fat diet-fed mice.[10,11,12]
- **Suppression of Lipogenesis:** Inhibition of MPST, resulting in increased H2S levels, leads to the downregulation of lipogenic genes, such as SREBP-1 and fatty acid synthase (FAS), thus reducing lipid accumulation in hepatocytes.[11,13]

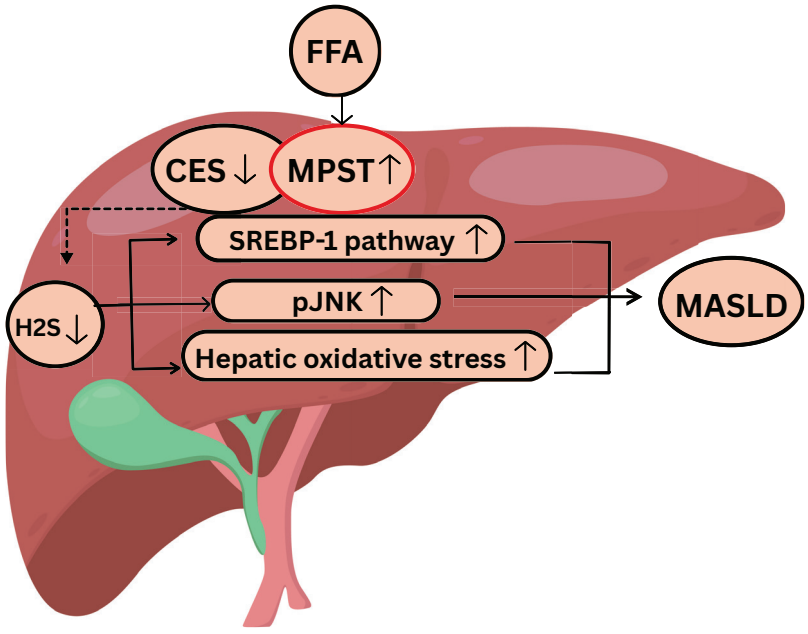

Fig 2. MPST Pathway.[6]

C. STING-IRF3 pathway

Stimulator of Interferon Genes (STING) is an endoplasmic reticulum membrane protein expressed across various tissues. It acts as a crucial link between upstream DNA sensors and downstream signaling molecules, including interferon regulatory factor 3 (IRF3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Activation of this pathway stimulates the production of type I interferons, providing potent antiviral effects.[6]

A high-fat diet or exposure to free fatty acids (FFAs) can upregulate STING and phosphorylated IRF3 in liver cells, leading to increased levels of p-p65/p65, pro-inflammatory cytokines, and apoptosis signals, along with disturbances in glycolipid metabolism. Silencing STING and IRF3 using small interfering RNAs (siRNAs) have been shown to reduce these inflammatory markers, normalize glycolipid metabolism, and suppress apoptosis.[6]

These findings suggest that the STING-IRF3 pathway plays a significant role in MASLD by regulating inflammation, apoptosis, and metabolic processes. Targeting this pathway could offer a novel therapeutic strategy for preventing the development of MASLD.[6]

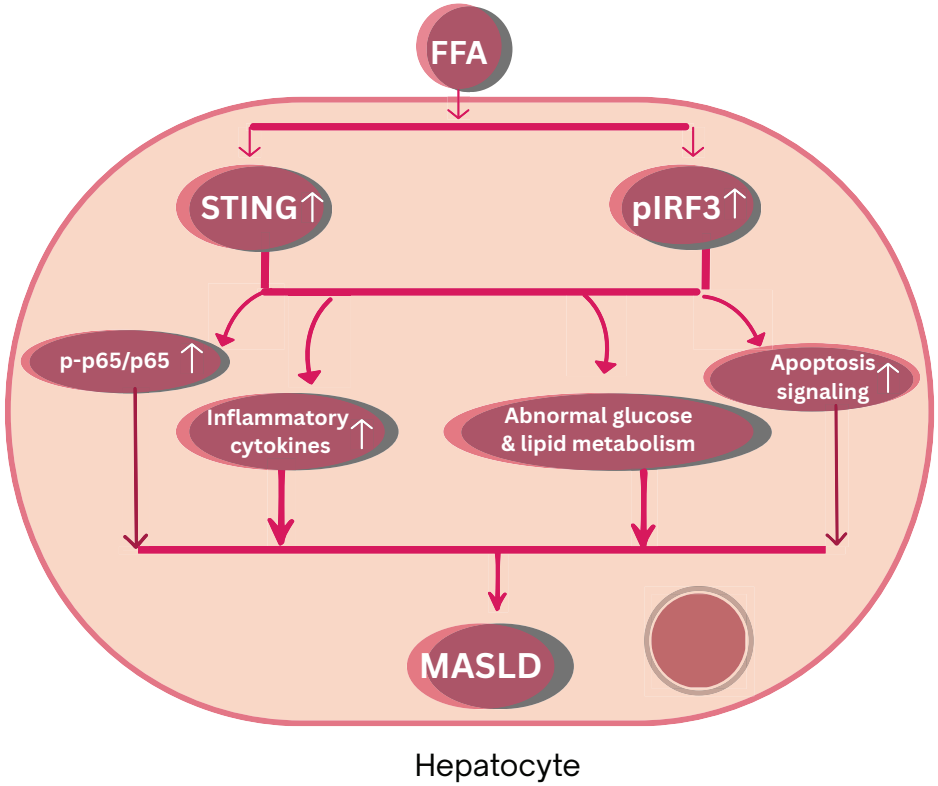

Fig 3. STING-IRF3 pathway.[6]

D. CRTC2-miR-34a pathway

The cAMP response element-binding protein (CREB)-regulated transcriptional coactivator (CRTC) family enhances the transcriptional activity of basic leucine zipper transcription factors. In the liver, CRTC2 is the primary isoform and plays a pivotal role in regulating gluconeogenesis.[6]

MicroRNA-34a (miR-34a) is a small, non-coding RNA molecule found in various cell types, including macrophages, endothelial cells, adipocytes, and liver cells. Sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide-dependent deacetylase, regulates numerous physiological processes, such as apoptosis, metabolism, immune response, oxidative stress, and mitochondrial function. The mammalian target of rapamycin complex 1 (mTORC1) act as a critical signaling hub that coordinates nutrient status and cell growth.[6]

A high-fat diet can upregulate CRTC2 expression in liver cells, which stimulates miR-34a production and suppresses SIRT1 expression, thereby reducing SIRT1-mediated deacetylation. This dysregulation contributes to the activation of

mTORC1 by inhibiting its natural inhibitor, the tuberous sclerosis complex (TSC). As a result, lipid accumulation is promoted through enhanced lipogenesis and reduced lipolysis, driving the progression of MASLD.[6]

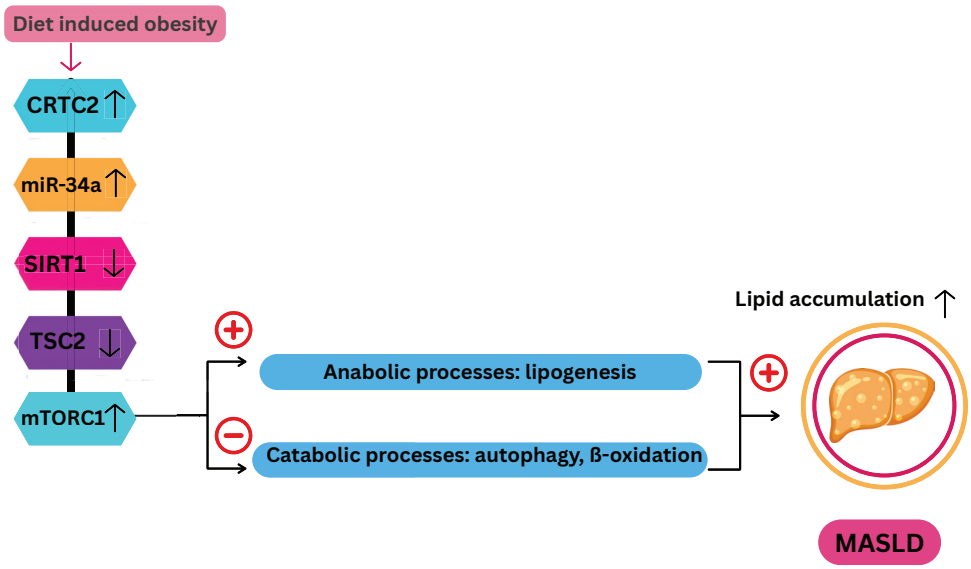

Fig 4. CRTC2-miR-34a pathway.[6]

E. AA1-TLR4-NF-κB-SAA1 feed-forward regulatory pathway

Serum amyloid A (SAA) is an apolipoprotein family differentially expressed in the body, with SAA1 primarily produced by liver cells. Under normal conditions, SAA levels are low but can rise sharply during acute-phase responses triggered by inflammation, infection, trauma, or cancer. Toll-like receptors (TLRs) are type I transmembrane receptors present on various cell membranes. They are released by host cells to activate intracellular pathways, leading to the production of proinflammatory cytokines, chemokines, and costimulatory molecules for defense against invading microorganisms.[6]

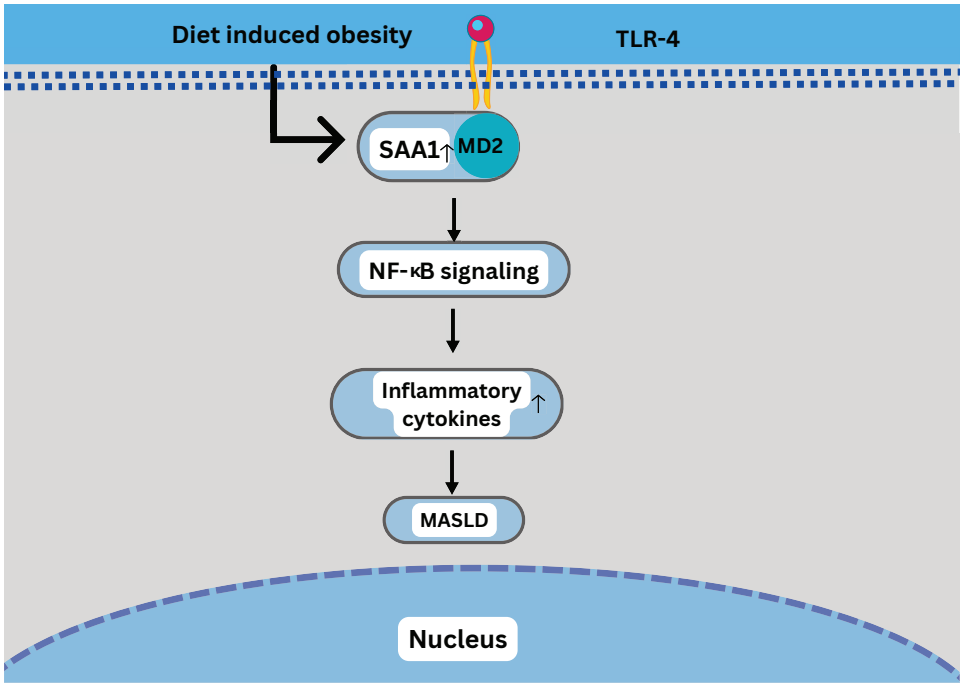

Fig 5. SAA1-TLR4-NF-κB-SAA1 feed-forward regulatory pathway.[6]

TLR4, a key subtype, recognizes viral structural and non-structural proteins. A high-fat diet can upregulate SAA1 expression in liver cells. SAA1 directly binds to TLR4 and myeloid differentiation 2 (MD2), inducing TLR4 internalization and activating NF-κB signaling. This process triggers the production of SAA1 and other inflammatory factors, promoting hepatic steatosis and intrahepatic inflammation, contributing to the progression of MASLD. The SAA1-TLR4-NF-κB-SAA1 feed-forward loop represents a potential target for MASLD intervention.[6]

F. OPG-ERK-PPAR-γ-CD36 pathway

Osteoprotegerin (OPG), a soluble glycoprotein belonging to the tumor necrosis factor (TNF) receptor superfamily, is expressed in multiple tissues, including the liver, bone, kidney, and lungs. Its role in hepatic lipid metabolism has garnered increasing attention due to emerging links with MASLD.[6]

Evidence suggests that a high-fat diet (HFD) or exposure to free fatty acids (FFAs) can induce OPG overexpression in hepatocytes. In models of OPG knockout mice, reintroduction of OPG leads to activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) and suppression of extracellular signal-regulated kinase (ERK) phosphorylation.6 This molecular shift is associated with upregulation of CD36, a fatty acid translocase responsible for facilitating lipid uptake into hepatocytes. The increased lipid influx driven by CD36 expression promotes hepatocyte steatosis and contributes to MASLD pathogenesis.[14–17]

PPAR-γ, a nuclear receptor with key roles in adipogenesis and lipid metabolism, is known to be activated by elevated FFAs and other metabolic stressors. While activation of PPAR-γ upregulates CD36 and enhances fatty acid uptake into hepatocytes, it is important to note that PPAR-γ agonists have also demonstrated beneficial effects on insulin sensitivity and may exert protective roles in MASLD, especially in the context of inflammation and fibrosis.18,19 Thus, the role of PPAR-γ in hepatic steatosis is complex and may vary depending on disease stage, cellular context, and co-existing metabolic factors.

ERK phosphorylation, part of the mitogen-activated protein kinase (MAPK) signaling cascade, plays a crucial role in regulating cell survival, proliferation, and metabolic adaptation. Although direct evidence linking OPG to ERK modulation in hepatocytes remains limited, metabolic dysregulation and lipid exposure have been shown to alter ERK activity, with downstream consequences for hepatic lipid metabolism. Decreased ERK phosphorylation, as observed in OPG-overexpressing models, may contribute to hepatocyte dysfunction and promote steatotic changes.[20,21]

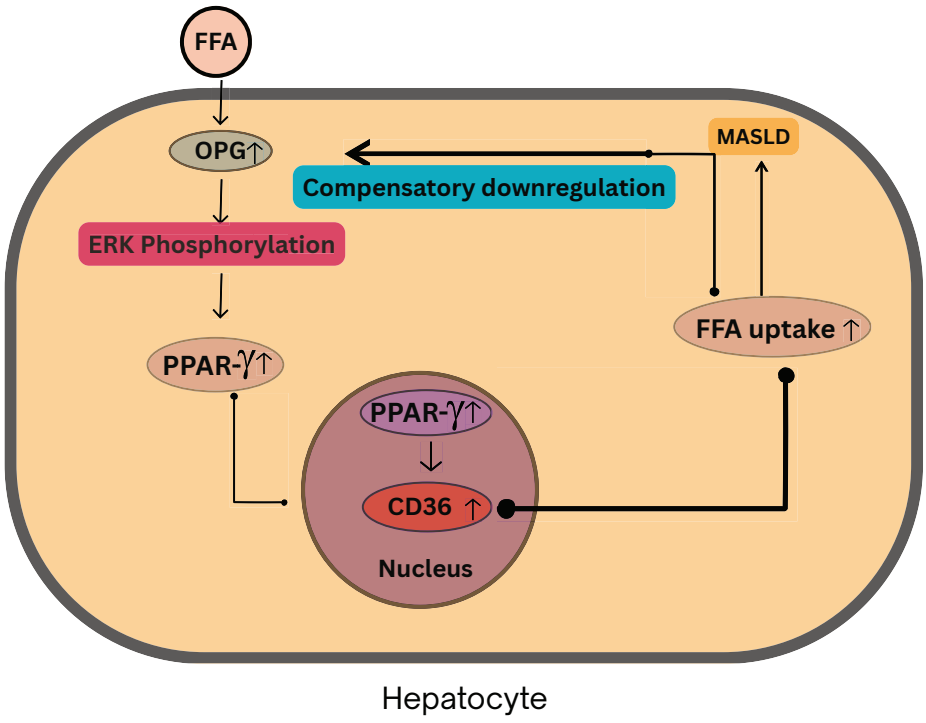

Fig 6. OPG-ERK-PPAR-γ-CD36 pathway.[6]

G. miR-122-SIRT1-LKB1/AMPK pathway

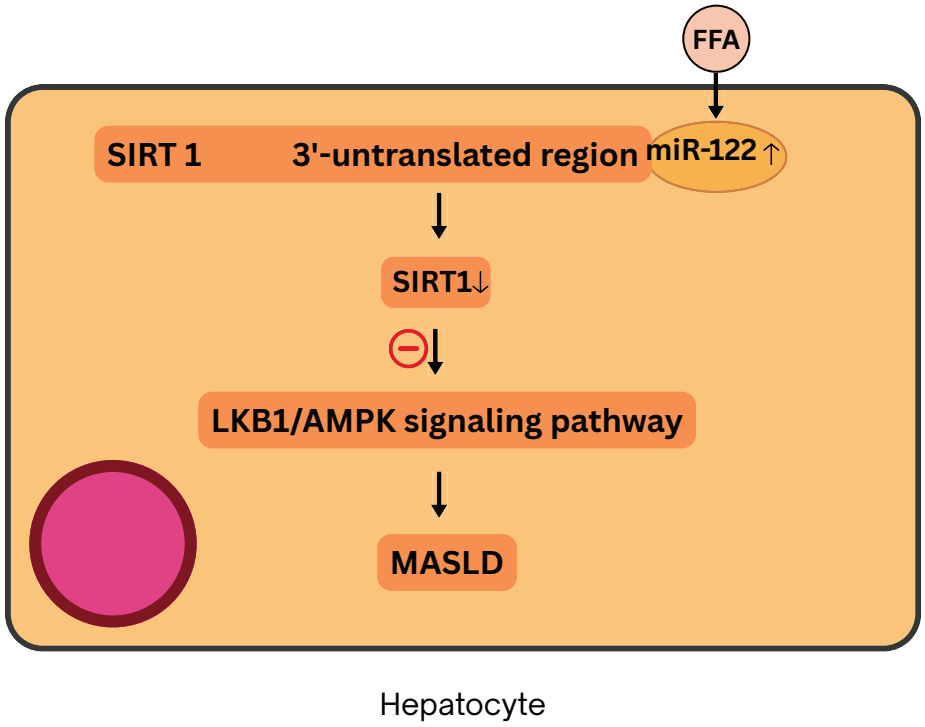

Fig 7. miR-122-SIRT1-LKB1/AMPK pathway.[6]

MicroRNAs (miRNAs) are small noncoding RNA molecules that regulate metabolic homeostasis through post-transcriptional mechanisms. Liver kinase B1 (LKB1) is a serine/threonine kinase and a key tumor suppressor in various cancer cells. As the upstream master kinase for 13 AMP-activated protein kinase (AMPK)-related kinases, LKB1 plays critical roles in cellular metabolism.[6]

A high-fat diet or free fatty acids (FFA) can upregulate miR-122 expression in hepatocytes. miR-122 directly binds to the 3′-untranslated region of SIRT1, suppressing its expression and inhibiting the LKB1/AMPK pathway. This suppression promotes lipogenesis and hepatocyte steatosis.[6]

Given its role in metabolic dysregulation, miR-122 holds potential as a diagnostic biomarker and therapeutic target for MASLD.[6]

H. SeP-AMPK/ACC pathway

Selenoprotein P (SeP) is a liver-produced glycoprotein responsible for transporting selenium to extrahepatic tissues. Elevated serum SeP levels are strongly associated with the severity and metabolic risk factors of MASLD. In both in vivo and in vitro MASLD models, SeP exacerbates the condition by inhibiting the AMPK/acetyl-CoA carboxylase (ACC) pathway.[6]

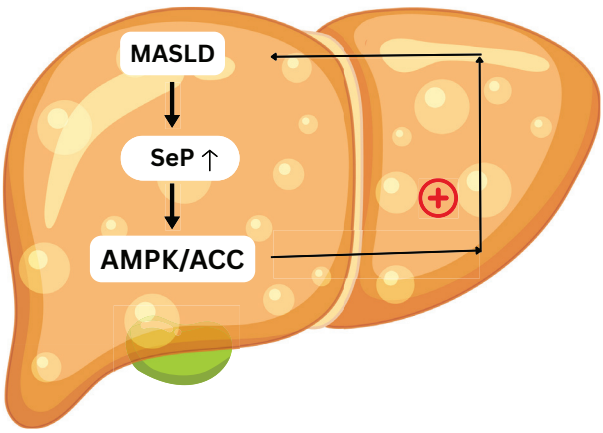

Fig 8. SeP-AMPK/ACC pathway.[6]

I. HIF-2α/PPARα pathway

Hypoxia-inducible factor-2α (HIF-2α) is widely expressed in endothelial cells of the lungs, intestine, and other tissues. Peroxisome proliferator-activated receptor α (PPARα), a ligand-activated nuclear receptor, is highly expressed in the liver. Under hypoxic conditions, HIF-2α becomes overexpressed in

steatotic liver cells, suppressing PPARα expression. This impairs mitochondrial function, inhibits fatty acid β-oxidation, and exacerbates lipid accumulation, worsening MASLD progression. Alleviating hypoxia may offer a therapeutic strategy for MASLD, with HIF-2α emerging as a potential treatment target.[6]

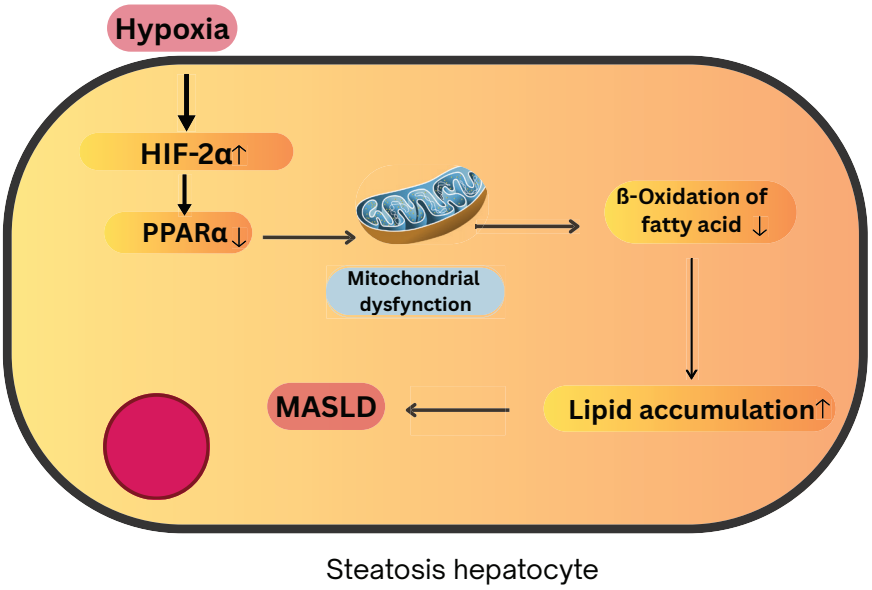

Fig. 9 HIF-2α/PPARα pathway.[6]

J. miR-665–3p-FNDC5/AMPKα pathway

Fibronectin type III domain 5 (FNDC5) is a type I transmembrane glycoprotein that can be cleaved to release irisin, an exercise-responsive peptide. A high-fat diet or free fatty acids (FFA) upregulate microRNA-665–3p (miR-665–3p) in liver cells, which binds to the 3′ untranslated region of FNDC5, suppressing its expression and inhibiting the AMPKα pathway. This disruption promotes oxidative stress, inflammation, and MASLD progression. Inhibition of miR-665–3p with an antagonist significantly reduces oxidative stress, inflammation, and liver dysfunction in vivo. Targeting miR-665–3p may offer a promising therapeutic strategy for MASLD by restoring FNDC5/AMPKα pathway activity.[6]

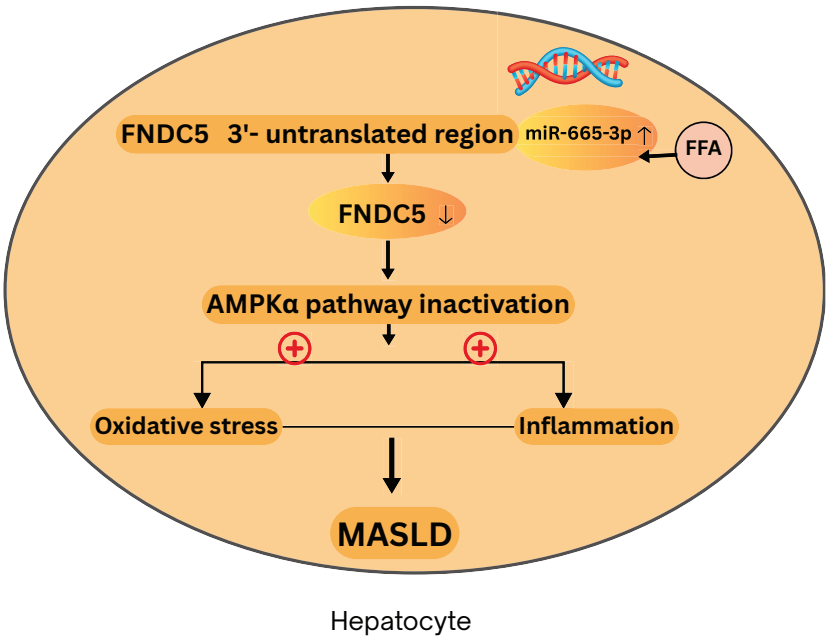

Fig 10. miR-665–3p-FNDC5/AMPKα pathway.6

K. CircScd1-JAK2/STAT5 pathway

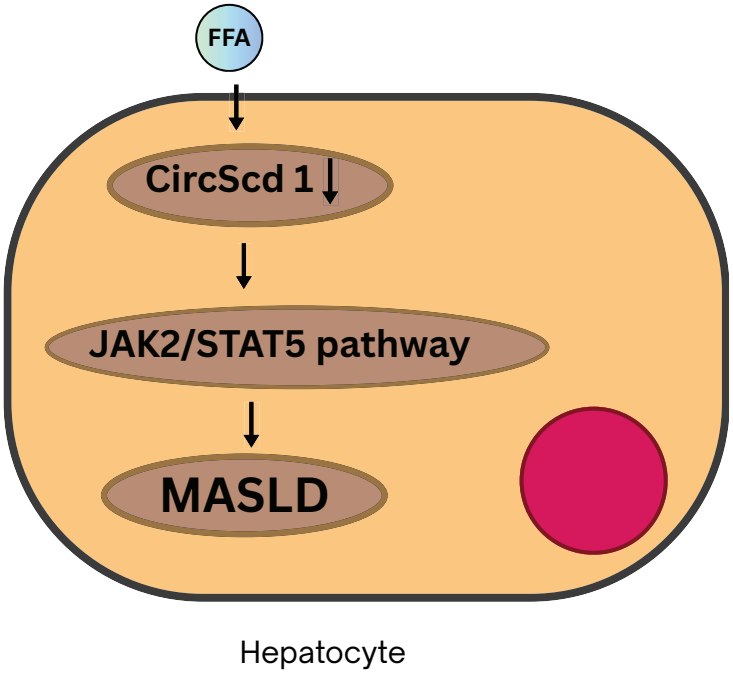

Fig. 11 CircScd1-JAK2/STAT5 pathway.[6]

Circular RNAs (CircRNAs) are a unique class of noncoding RNA formed by back-splicing, with CircScd1 being one example. Janus kinase 2 (JAK2) is a non-receptor tyrosine kinase involved in signaling for hormones and cytokines, while STAT5, a member of the STAT protein family, mediates immune response, cell proliferation, and differentiation.[6]

A high-fat diet or palmitate reduces CircScd1 expression in liver cells, promoting MASLD progression through the JAK2/STAT5 pathway. However, the exact mechanism linking CircScd1 to this pathway remains unclear. Targeting this interaction may offer a potential therapeutic strategy for MASLD.[6]

Although the effect of high-fat diets on CircScd1 expression and its regulatory role in MASLD via the JAK2/STAT5 pathway has been described, direct evidence linking high-carbohydrate diets to similar changes remains limited. A study by Kawabata et al demonstrated that high-fructose feeding upregulates Scd1 expression through carbohydrate response element-binding protein (ChREBP)-mediated activation, contributing to hepatic triglyceride accumulation in rats.[22] In contrast, CircScd1—a circular RNA derived from Scd1—has been shown to exert protective effects in MASLD by activating the JAK2/STAT5 pathway and inhibiting lipid droplet formation.[23] However, whether high-carbohydrate diets affect CircScd1 levels in a manner that influences this signaling axis remains unexplored. Further investigation is warranted to clarify the relationship between dietary carbohydrate intake and CircScd1-mediated regulation of hepatic lipid metabolism.

Conclusion

MASLD is the most prevalent chronic liver disease globally, posing significant health concerns due to its potential to progress to severe conditions such as inflammation, fibrosis, cirrhosis, and liver cancer. It also increases the risk of cardiovascular diseases, metabolic disorders, and certain cancers. Previously termed metabolic dysfunction-associated fatty liver disease (MAFLD), the condition was redefined in 2023 to include metabolic dysfunction-associated steatohepatitis (MASH), highlighting the role of metabolic and systemic factors.

MASLD develops due to a complex interplay of metabolic, genetic, and environmental factors, including age, gender, diet, alcohol consumption, and metabolic conditions such as obesity, diabetes, and hypertension.

MASLD progression involves complex molecular and metabolic pathways influenced by various regulatory factors. Key contributors include the inhibition of apoA5 secretion, leading to triglyceride accumulation and hepatic steatosis, and elevated SeP levels, which exacerbate the disease by impairing lipid metabolism. Hypoxia-induced HIF-2α overexpression suppresses PPARα, worsening lipid accumulation and mitochondrial dysfunction. Additionally, microRNA-665–3p disrupts the FNDC5/AMPKα pathway, promoting oxidative stress and inflammation. Emerging therapeutic targets, such as miR-665–3p antagonism, SeP inhibition, and alleviating hypoxia, hold promise for managing MASLD by restoring metabolic balance and preventing disease progression.

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