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REVIEW

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Adipokines regulate the development and progression of MASLD through organellar oxidative stress

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Abstract

The prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD), which is increasingly being recognized as a leading cause of chronic liver pathology globally, is increasing. The pathophysiological underpinnings of its progression, which is currently under active investigation, involve oxidative stress. Human adipose tissue, an integral endocrine organ, secretes an array of adipokines that are modulated by dietary patterns and lifestyle choices. These adipokines intricately orchestrate regulatory pathways that impact glucose and lipid metabolism, oxidative stress, and mitochondrial function, thereby influencing the evolution of hepatic steatosis and progression to metabolic dysfunction–associated

Abbreviations: Akt, protein kinase B; AML12, murine liver cells; AMPK, AMP-activated protein kinase; ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; BAT, brown adipose tissue; BiP, immunoglobulin heavy chain-binding protein; BMI, body mass index; C3, complement component 3; Cat, catalase; CCL2, CC-chemokine ligand 2; CCRL2, CC chemokine receptor-like 2; CHIP, C-terminal Hsc70-interacting protein; CHOP, CCAAT-enhancer-binding protein (C/EBP) homologous protein; CMKLR1, chemokine-like receptor 1; DRP1, dynamin-related protein 1; eIF2α, eukaryotic translation initiation factor 2 alpha; ER, endoplasmic reticulum; ERAD, ER-associated degradation; ERK1/2, extracellular signal-regulated kinase1/2; FAS, fatty acid synthase; FFAs, free fatty acids; FNDC5, fibronectin type III domain-containing protein 5; FOXO, forkhead box O; FOXO3, forkhead box transcription factor 3; GPR1, G-protein coupled receptor 1; GPX1, glutathione peroxidase 1; GRP78, 78-kDa glucose-regulated protein; GSH/GSSG, glutathione/oxidized glutathione; GST, glutathione-S-transferase; HepG2, human liver cancer cells; HFD, high-fat diet; HNRNPA1, heterogeneous nuclear ribonucleoprotein A1; I/R, ischemia/reperfusion; IL-1β, interleukin-1β; IL-6, interleukin-6; IR, insulin resistance; IRE1, inositol-requiring enzyme 1; JAK2, Janus kinase 2; JNK, c-Jun N-terminal kinase; KCs, Kupffer cells; LCAD, long-chain acyl-CoA dehydrogenase; LR, leptin resistance; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MDA, malondialdehyde; MPO, myeloperoxidase; MTP, mitochondrial transmembrane potential; NF-κB, nuclear factor-κB; NLRP3, NLR family pyrin domain-containing 3; NOS, nitric oxide synthase; NOX2, NADPH oxidase-2; Nrf2, nuclear factor erythroid 2-related factor 2; Per1, period 1; PERK, PKR-like ER kinase; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1-alpha; PGC-1β, proliferator-activated receptor-gamma coactivator 1-beta; PI3K, phosphatidylinositol 3-kinase; PPARα, peroxisome proliferator-activated receptor-α; RBP4, retinol-binding protein 4; ROS, reactive oxygen species; SCD1, stearoyl-CoA desaturase-1; SIRT3, Sirtuin 3; SOD, superoxide dismutase; SOD2, superoxide dismutase 2; SREBP, sterol regulatory element-binding protein; STAT3, signal transducer and activator of transcription 3; T2DM, type 2 diabetes mellitus; TBARS, thiobarbituric acid reactive substances; TFAM, mitochondrial transcription factor A; TG, triglyceride; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; UCP2, uncoupling protein 2; UPR, unfolded protein response; VLDLR, very low-density lipoprotein receptor; WAT, white adipose tissue; XBP1, X-box binding protein 1; XBP1s, spliced X-box binding protein 1.

Ke Zhao and Heng Zhang contributed equally to this work.

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steatohepatitis (MASH). This review examines recent data, underscoring the critical interplay of oxidative stress, reactive oxygen species, and redox signaling in adipokine-mediated mechanisms. The role of various adipokines in regulating the onset and progression of MASLD/MASH through mitochondrial dysfunction and endoplasmic reticulum stress and the underlying mechanisms are discussed. Due to the emerging correlation between adipokines and the development of MASLD positions, these adipokines are potential targets for the development of innovative therapeutic interventions for MASLD management. A comprehensive understanding of the pathogenesis of MASLD/MASH is instrumental for identifying therapies for MASH.

Keywords: adiponectin, endoplasmic reticulum stress, fatty liver, FGF-21, mitochondrial dysfunction

HIGHLIGHTS

1. The occurrence and development of MASLD are closely related to oxidative stress.
2. Adipokines directly or indirectly impair mitochondrial and endoplasmic reticulum function in the liver, initiating and promoting the development of MASLD.
3. Adipokine dysregulation has emerged as a pivotal driving force behind the progression of MASLD.
4. A thorough understanding of the functions of adipokines will provide potential avenues for discovering therapies for MASLD/MASH.

INTRODUCTION

NAFLD is a chronic metabolic liver disorder characterized by excessive fat accumulation in the livers of individuals who consume alcohol in minimal quantities or who do not consume alcohol. This condition spans a spectrum of liver diseases, including NAFL, NASH, liver fibrosis with a fatty component, and cirrhosis.[1] NAFLD may eventually progress to liver failure or even HCC.[2] Presently, NAFLD is the foremost cause of chronic liver disease worldwide, which is consistent with the increasing global prevalence of diabetes and metabolic syndrome.[3] The primary contributing factors of NAFLD include diabetes, obesity, and hyperlipidemia.[4] Traditionally, NAFLD has been viewed as the hepatic component of metabolic syndrome; NAFLD was recently reconceptualized by an international consortium of experts as metabolic dysfunction–associated steatotic liver disease (MASLD),[5] which is not substantially different from the metabolic dysfunction–associated fatty liver disease (MAFLD) proposed by experts in the Asia-Pacific region.[6] Moreover, NASH was reconceptualized as metabolic dysfunction–associated steatohepatitis (MASH).[5] This redefinition emphasizes the close link between hepatic steatosis and metabolic disorders, including type 2 diabetes mellitus (T2DM), obesity, and dyslipidemia, which lead to an increased risk of progression to more advanced stages, such as NASH and fibrosis.[7]

Globally, it is estimated that ~25% of the adult population suffers from MASLD, with the incidence increasing to 40%–60% in overweight and obese individuals.[8] Data from epidemiological studies conducted in 2020 indicate that the prevalence of MASLD in China has risen to 29.88%, which is consistent with the increase in obesity rates.[9,10] Theories regarding the pathogenesis of MASLD have evolved from the classical "two-hit" theory to the more nuanced "multiple-hit" hypothesis, although the underlying mechanism remains to be fully clarified. According to the initial "it" theory, triglyceride (TG) accumulation due to a variety of factors represents a pivotal factor in the onset of MASLD. The progression of MASLD to MASH and advanced stages is promoted by the simultaneous accumulation of various factors, including genetic and epigenetic changes, inflammatory cytokines, adipokines, alterations in the gut microbiome, oxidative stress, and mitochondrial dysfunction.[11,12] In particular, oxidative stress plays a central role in liver damage and disease progression. External factors, such as a sedentary lifestyle, an imbalanced diet, and the use of pharmaceuticals, as well as internal factors, such as obesity and diabetes, are known to exacerbate oxidative stress in liver pathologies.[13] Researchers have explored these concurrent factors as potential therapeutic targets for MASLD.[1,14] Considering the intricate pathogenesis of MASLD, novel therapeutic interventions aimed at mitigating lipotoxicity and reducing hepatic inflammation are urgently needed.

SIGNIFICANCE OF OXIDATIVE STRESS IN THE PATHOGENESIS OF MASLD

Evidence emphasizing the central role of oxidative stress in both the development and progression of MASLD is increasing.[15,16] Disruption of fatty acid metabolism, coupled with insulin resistance, leads to the accumulation of fatty acids and TGs in hepatocytes. Oxidative stress exacerbates these disruptions, precipitating the onset of NASH and inducing progression to liver fibrosis and steatohepatitis.[17,18] Consequently, reducing oxidative stress has emerged as a key strategy for the management of MASLD.[19,20] When oxidative stress is elevated, the amount of reactive oxygen species (ROS) generated surpasses the amount of ROS eliminated, triggering lipid peroxidation and cytokine production. This imbalance results in hepatocellular injury and fibrosis[21] and accelerates the transition from simple steatosis to MASH.[22] Oxidative stress is known to induce mitochondrial dysfunction, endoplasmic reticulum (ER) stress, lipopolysaccharide (LPS)-induced Toll-like receptor 4 (TLR4)-dependent inflammatory cytokine release, and iron overload. These factors initiate a series of signaling cascades that culminate in inflammation, cellular death, and fibrosis (Figure 1).[11]

Influence of mitochondrial dysfunction on MASLD

Mitochondrial dysfunction significantly influences MASLD by disrupting lipid metabolism, thereby upsetting hepatic homeostasis. This dysfunction results in the overproduction of free radicals, leading to lipid peroxidation and cellular death, and thus contributes to the development of MASH.[23,24] Research indicates that, regardless of the occurrence of steatosis, obese individuals exhibit increased hepatic lipid levels, which increases their mitochondrial respiratory capacity. While this adaptation may serve as a defense mechanism against the onset of MASLD, the resulting mitochondrial electron leakage could inadvertently promote superoxide radical formation, aggravating oxidative stress in hepatic cells. This scenario can cause a decrease in mitochondrial efficacy, potentially accelerating MASLD progression to MASH. Patients with MASLD exhibit a degree of mitochondrial adaptability; however, the loss of this adaptability might be a pivotal factor in the progression to MASH.[25] Furthermore, liver mitochondria in patients with MASH display ultrastructural abnormalities, in addition to a reduction in respiratory chain complex activity. This reduced chain activity can cause the accumulation of ROS, leading to further oxidation of lipids and the generation of lipid peroxides. These peroxides can then lead to steatohepatitis, necrosis, inflammation, and fibrosis.[26,27] As a primary source of ROS, mitochondria have a detrimental effect on hepatic homeostasis by inducing lipid peroxidation, stimulating HSCs, promoting hepatocyte apoptosis, and triggering both innate and adaptive immune responses, thus facilitating the progression from MASLD to MASH.[28]

Effects of ER stress on MASLD

Disorders of hepatic lipid metabolism are intricately linked with disturbances in ER homeostasis. The unfolded protein response (UPR), a signaling pathway, is activated in response to chronic ER stress and reestablishes ER stability.[29] Initiation of the UPR predominantly relies on the activation of 3 ER transmembrane stress sensors: inositol-requiring enzyme 1 (IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6).[30,31] Chronic UPR activation ensues when the ER lumen becomes overloaded with improperly folded proteins, exceeding the capacity of the aforementioned pathways to effectively these proteins. This excessive and prolonged ER stress, combined with adaptive response failure, is a pivotal factor in the progression of MASLD.[32] Sustained UPR activation in the liver has been shown to play a causative role in MASLD progression by promoting the induction of lipogenesis, perturbation of mitochondrial activity, and alternations in insulin signaling.[33,34]

Notably, studies of the mechanisms underlying the impacts of UPR effectors on hepatic steatosis have yielded complicated, sometimes contradictory results. X-box binding protein 1 (XBP1), a major molecular node in the ER stress signaling pathway, may function as a prolipogenic or antilipogenic gene in different animal models, including genetic ablation models and animals in which an adenovirus is used to deliver XBP1 to the liver.[35,36] A study revealed that inducible selective deletion of spliced X-box binding protein 1 (XBP1s) in the liver results in marked hypocholesterolemia and hypotriglyceridemia, secondary to decreased production of lipids in the liver. XBP1s is associated with the safe storage of excess lipids such as TGs in lipid droplets.[35] However, other studies indicate that ER stress activation leads to IRE1 pathway activation, resulting in the production of XBP1s, which increases ER protein folding, secretion, ER-associated degradation (ERAD), and lipid synthesis. XBP1s increases period 1 (Per1) transcription, which further exacerbates MASLD progression by increasing the expression of lipogenic genes such as sterol regulatory element-binding protein (SREBP)-1c.[37] Intracellular lipid accumulation not only triggers lipid peroxidation but also promotes ER stress. This stress impedes VLDL/TG secretion through the IRE1α-XBP1 pathway, promotes hepatic steatosis,[38] and, through the PERK-eukaryotic translation initiation factor 2 alpha (eIF2α)-activating

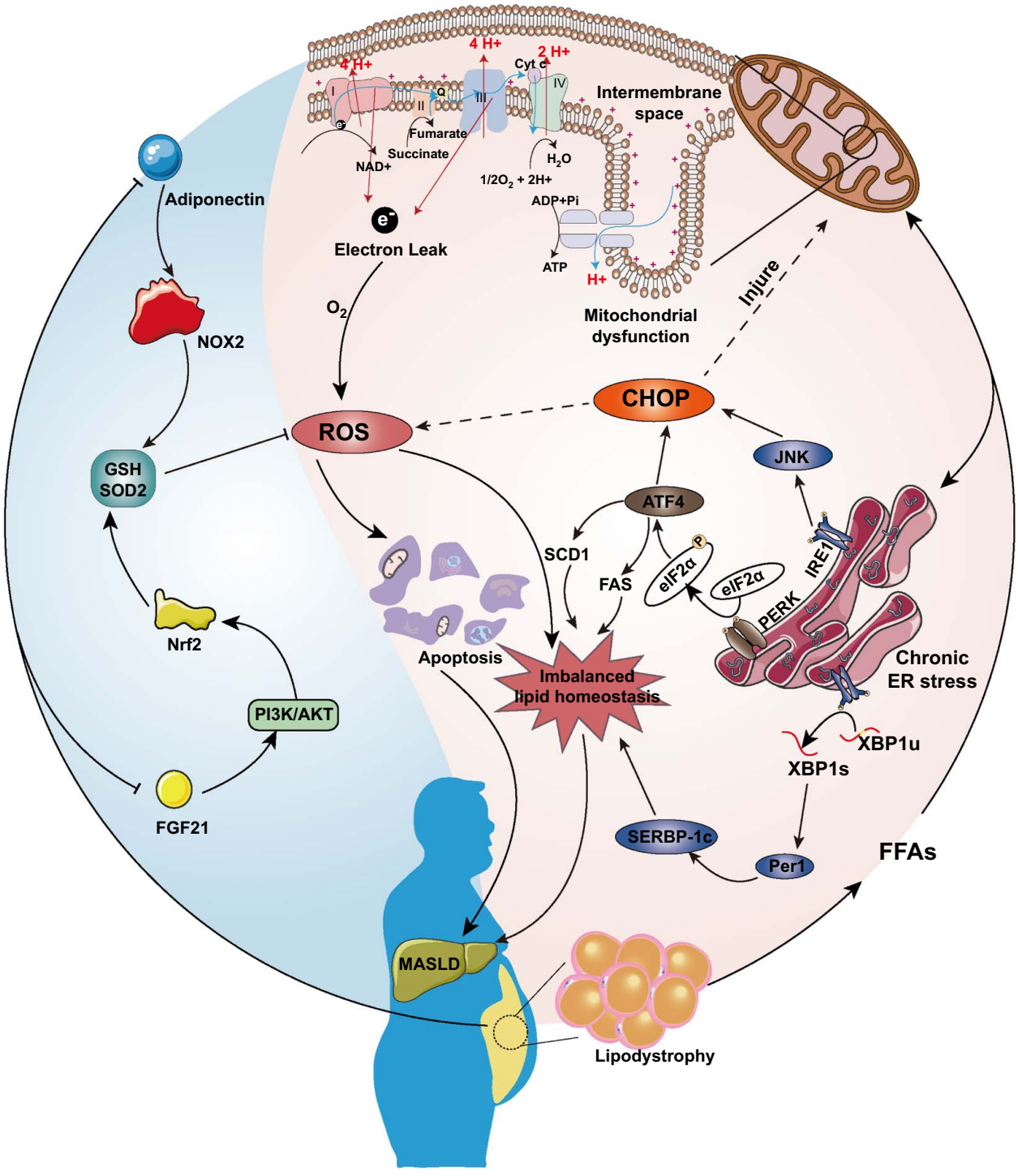


FIGURE 1 Free fatty acids initiate cellular dysfunction and the role of several adipokines in MASLD. Excessive free fatty acids are known to induce mitochondrial dysfunction and endoplasmic reticulum stress, which initiate a series of signaling cascades that culminate in imbalanced lipid homeostasis and apoptosis. In addition, adiponectin and FGF-21 prevent the generation of ROS by enhancing the activity of GSH and SOD2, thereby reducing hepatic damage and steatosis. Abbreviations: Akt, protein kinase B; ATF4, activating transcription factor 4; CHOP, CCAAT-enhancer-binding protein homologous protein; eIF2α, eukaryotic initiation factor 2 alpha; ER, endoplasmic reticulum; FAS, fatty acid synthase; FFAs, free fatty acids; GSH, glutathione; IRE1, inositol-requiring enzyme 1; JNK, c-Jun N-terminal kinase; MASLD, metabolic dysfunction–associated steatotic liver disease; NOX2, NADPH oxidase-2; Nrf2, nuclear factor erythroid 2–related factor 2; Per1, period 1; PERK, PKR-like ER kinase; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; SCD1, stearoyl-CoA desaturase-1; SOD2, superoxide dismutase 2; SREBP-1c, sterol regulatory element-binding protein-1c; XBP1s, spliced X-box binding protein 1; XBP1u, unspliced X-box binding protein 1.

transcription factor 4 (ATF4) pathway, increases the activity of key enzymes such as stearoyl-CoA desaturase-1 (SCD1) and fatty acid synthase (FAS), further aggravating the imbalance of lipid homeostasis in the liver.[39] While a change in XBP1 expression may reflect either adaptive protection of the liver or disease progression, CCAAT-enhancer-binding protein (C/EBP) homologous protein (CHOP) expression seems to be a robust marker of detrimental effects. In a study on all stages of MASLD, namely, simple steatosis, MASH, fibrosis/cirrhosis, and HCC, hepatic CHOP expression was strongly correlated with disease progression. Moreover, the contribution of CHOP to MASLD progression has been shown in genetic deletion mouse models.[32]

ADIPOKINES AND THEIR ROLE IN MASLD THROUGH OXIDATIVE STRESS

Adipose tissue, once regarded merely as a passive energy storage site, is now recognized as a dynamic endocrine organ; it secretes a myriad of biologically active peptides and proteins, collectively termed adipokines, that exert significant systemic effects, especially on the liver.[40] Under physiological conditions, adipokines interact with various organs, including the brain, liver, skeletal muscle, and endocrine pancreas. Adipokines are involved in regulating glucose and lipid metabolism, improving insulin resistance, and maintaining overall homeostasis. In obesity and under conditions of metabolic imbalance, expanded adipose tissue and altered adipocyte function lead to adipokine dysregulation. This disrupts adipokine secretion and function, aggravating ER and oxidative stress, thereby driving chronic low-grade inflammation and worsening metabolic dysregulation and insulin resistance.[41] Adipose tissue is a major source of oxidative stress and ROS,[42–44] and the imbalance of inflammatory adipocytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and resistin contributes to ROS formation and oxidative stress.[45,46] Research conducted on multiethnic cohorts has established a connection between plasma levels of thiobarbituric acid reactive substance (TBARS), an oxidative stress biomarker, and visceral adipose tissue; this research demonstrated a strong correlation of visceral adipose tissue with body composition parameters, including body mass index (BMI), total body fat, and central obesity, in Chinese populations.[47] Increases in the levels of free fatty acids (FFAs), proinflammatory cytokines, and adipokines in adipose tissue contribute to increased lipid accumulation in the liver. Excessive FFAs are known to induce mitochondrial dysfunction and increase oxidative stress in the liver, resulting in uncoupled oxidative phosphorylation; furthermore, they activate HSCs, thus accelerating progression to MASH and cirrhosis.[8]

Adipose tissue can be divided into 2 distinct types: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT functions as the primary organ for lipid storage and plays a central role in maintaining systemic energy homeostasis by regulating metabolic adaptability and governing the allocation of lipids to different organs. A previous study demonstrated that the presence of very large adipocytes is correlated with increased inflammatory activity and the incidence of MASLD, T2DM, and other metabolic disorders.[48] Adipocyte hypertrophy is accompanied by dysregulated adipocyte differentiation, enlargement of lipid droplets, an impaired insulin response and glucose uptake, increased FFA secretion, abnormal adipocyte osmolarity sensors, increased release of proinflammatory cytokines, exacerbation of hypoxia, and excessive collagen deposition.[49] In addition, WAT releases a variety of adipokines, influencing energy equilibrium and broader regulation of glucose and lipid metabolism in distant target tissues, including the liver, muscles, and brain.[50] During prolonged metabolic stress resulting from nutritional excess, adipose tissue dysfunction arises, which is characterized by reduced metabolic adaptability and a compromised lipid buffering capacity. This condition leads to the uncontrolled release of fatty acids from adipose tissues, sparking systemic maladaptive responses to overnutrition, disrupting lipid mobilization, and increasing inflammation. Furthermore, this inflammation in adipose tissue leads to an atypical cytokine secretion profile.[51] In response to overnutrition, adipose tissue undergoes remodeling on the basis of mass and quantity, altering the secretion patterns of adipokines and proinflammatory cytokines.[52]

The dysregulation of metabolic and immunoregulatory adipokines in dysfunctional adipose tissue results in the rerouting of fatty acids to other “ectopic” tissues, including the liver.[53] Accumulating evidence suggests that multilevel crosstalk between adipose tissue and the liver coordinates whole-body energy metabolism. This communication acts as a key player in modulating the initiation and development of metabolic diseases through the secretion of an array of adipokines and hepatokines. The FGF21-adiponectin axis functions as the key mediator of the crosstalk between the liver and adipose tissue to exert beneficial effects on the maintenance of energy consumption homeostasis.[54,55] In addition, adipose tissue can communicate with the liver by regulating the flow of lipids to the liver, producing adipokines and hormones that affect the function of liver cells, causing MASLD.[56] One study addressed the interaction between adipose tissue and the liver from an adipocentric perspective, highlighting the contribution of adipose tissue dysfunction to the development of MASLD.[51] Understanding the crosstalk between adipose tissue and the liver from the perspective of adipokines is important.

A growing body of research indicates that, compared with healthy individuals, individuals with MASLD/MASH exhibit changes in the levels of adipokines, which play a pivotal role in the onset and progression of the disease by modulating chronic liver inflammation.[57,58] Within this context, attention has been increasingly focused on adipokines secreted by cells in adipose tissue, including adipocytes, stromal cells, and/or immune cells, over the past decade. This interest stems from the capacity of adipokines to induce metabolic dysfunction.[58–61] While the levels of the majority of adipokines are elevated in obesity, fostering inflammatory responses, some adipokines may serve as anti-inflammatory regulators.[62] Adipokines can influence liver insulin sensitivity and lipid metabolism through an endocrine mechanism; they regulate oxidative stress, inflammation, fibrosis, and apoptosis-related signaling pathways intimately linked to MASH. Concurrently, adipokines can directly activate or inhibit pertinent signaling pathways, thereby influencing processes such as inflammation and fibrosis, consequently influencing the course of MASLD.[11] Table 1 summarizes the main characteristics of the adipokines mentioned in this review that initiate and drive the progression of MASLD/MASH.

Adiponectin

Adiponectin, the most abundant adipokine in the human body, is a monomeric glycoprotein secreted by adipocytes; it can be modified to form various multimeric subtypes with different molecular weights, including low-molecular-weight trimers, medium-molecular-weight hexamers, and high-molecular-weight 12–32-mers, and can enter the bloodstream; the high-molecular-weight subtype is considered the most biological subtype of adiponectin.[108] The actions of adiponectin are mediated by transmembrane receptors (AdipoR1 and AdipoR2), with AdipoR1 being highly expressed in skeletal muscle and AdipoR2 being expressed primarily in the liver.[109]

Adiponectin affects the liver by binding to AdipoR1 and AdipoR2 (Figure 2), which interact with downstream adaptor proteins through the PH domain and leucine zipper domain. The activation of AdipoR1 or AdipoR2 leads to the activation of the AMP-activated protein kinase (AMPK) and peroxisome proliferator–activated receptor-α (PPARα) signaling pathways. These interactions, in addition to interfering with insulin signaling pathways, increase hepatic insulin sensitivity, promote hepatic fatty acid oxidation, and reduce hepatic lipid accumulation.[63,64] Furthermore, AdipoR2 can inhibit the release of proinflammatory cytokines such as TNF-α, IL-6, and interferon-γ and ROS by activating the AMPK and PPARα signaling pathways, resulting in anti-inflammatory activity.[65]

Adiponectin also exerts hepatoprotective effects by activating the AMPK/c-Jun N-terminal kinase (JNK)/extracellular signal–regulated kinase 1/2 (ERK1/2) signaling pathway, inhibiting the nuclear factor-κB (NF-κB) signaling pathway, and reducing oxidative stress and the activation of the NLR family pyrin domain–containing 3 (NLRP3) inflammasome mediated by palmitic acid esters.[66] Research has shown that adiponectin can reduce malondialdehyde (MDA) levels and NADPH oxidase-2 (NOX2) levels, increase superoxide dismutase (SOD) activity, increase the glutathione/oxidized glutathione (GSH/GSSG) ratio, and increase TG levels in human liver cancer cells (HepG2 cells); additionally, it can alleviate oxidative stress and mitigate HepG2 cell damage by regulating NOX2 expression.[67]

The pivotal role of adiponectin in MASH has been corroborated in animal models. The loss of C-terminal Hsc70-interacting protein (CHIP) in mice causes oxidative stress, insulin resistance, and hepatic inflammation. Adiponectin overexpression, through the activation of the AMPK-forkhead box O (FOXO) signaling axis and its predominance over detrimental oxidative stress and JNK signaling, inhibits hepatic microvesicular steatosis, thus slowing the progression of MASLD/MASH.[110] In addition, increasing epidemiological evidence indicates an association between MASLD/MASH and the risk of HCC development.[2] Adiponectin administration exerts significant antitumor effects and significantly improves liver function and oxidative status. The results of a previous study revealed that adiponectin treatment significantly improved the hepatic GSH concentration and GST activity.[68]

Mitochondrial dysfunction is one of the mechanisms underlying lipid-mediated apoptosis in hepatocytes, primarily due to reduced activity of the mitochondrial respiratory chain. A previous study suggested that adiponectin reduces mitochondrial lipid peroxidation levels and restores mitochondrial respiratory chain function by increasing the expression of mitochondrial inner uncoupling protein 2 (UCP2).[69] Smad3 signaling may regulate both the mitochondrial apoptosis pathway and the ATF4-CHOP apoptosis pathway. Adiponectin can significantly suppress increases in Smad3 phosphorylation, indicating that it protects mitochondrial function and ER stress by inhibiting Smad3 signaling.[70] Another study revealed that adiponectin treatment restores the activity of mitochondrial respiratory chain complexes and reduces mitochondrial lipid peroxidation levels by regulating mitochondrial function, thereby reducing hepatocyte damage and inhibiting hepatic lipid apoptosis.[71]

Leptin

Under normal leptinemia conditions, leptin plays a pivotal role in mitigating fat accumulation and enhancing insulin sensitivity by curbing hepatic glucose and lipid

TABLE 1 Main characteristics of adipokines involved in the pathophysiology of MASLD/MASH

Adipokine	General function	Role in MASLD/MASH	Reference(s)
Adiponectin	Promotes fatty acid oxidation Inhibits the release of proinflammatory cytokines Activates the AMPK/JNK/ERK1/2 pathway and inhibits the NF-κB pathway Reduces MDA and NOX2 levels Restores mitochondrial respiratory chain function by upregulating UCP2 expression Reduces GSH concentrations and GST activity Suppress Smad3 phosphorylation	Increases insulin sensitivity Inhibits apoptosis in hepatic cells Reduces oxidative stress Exerts anti-inflammatory effects	[63–71]
Leptin	Forms peroxynitrite Increases iron content in the liver	Increases oxidative stress Activates KCs	[72,73]
FGF21	Suppress chronic activation of the ATF4/CHOP pathway Activates the AMPK-SIRT1 pathway Increases Nrf2-mediated antioxidant capacity by activating the PI3K/Akt pathway Counterbalances fatty acid deposition Increases the expression of antioxidant genes Increases mitochondrial β-oxidation	Increases hepatic insulin sensitivity Enhances mitochondrial oxidative Reduces endoplasmic reticulum stress Inhibits hepatic steatosis	[74–79]
RBP4	Increases the expression of PGC-1β and SREBP-1c Increases mitochondrial lipid oxidation Promotes the release of proinflammatory cytokines	Promotes de novo lipogenesis and steatosis Exerts proinflammatory effects	[80–82]
Irisin	Regulates the PI3K/Akt and AMPK pathways Decreases the production of reactive oxygen species Increases the stability of HNRNPA1 Suppresses mitochondrial fission and stimulates mitochondrial biogenesis Reduces iron overload and inhibits ferroptosis	Inhibits lipid accumulation Alleviates oxidative stress	[83–87]
Chemerin	Regulates the antioxidant defense system Lowers the levels of inflammatory proteins	Reduces oxidative stress Exerts anti-inflammatory effects	[88,89]
Vaspin	Induces the phosphorylation of components of the Akt pathway Increases insulin sensitivity	Suppresses apoptosis Prevents metabolic dysfunction	[90–92]
Apelin	Reduces insulin resistance Activates the PI3K/Akt pathway	Decreases steatosis Reduces oxidative stress	[93,94]
Resistin	Inhibits the phosphorylation of 5′ adenosine monophosphate–activated protein kinase α Promotes the synthesis of proinflammatory cytokines	Promotes lipid accumulation Increases endoplasmic reticulum stress Exerts proinflammatory effects	[95–97]
Visfatin	Inhibits insulin signaling Increases endoplasmic reticulum stress	Promotes insulin resistance Exerts proinflammatory effects	[98,99]
IGF-1	Improves mitochondrial function Decreases lipid peroxidation	Reduces oxidative stress Improves hepatic function	[100–102]
Adipsin	Reduces CHOP mRNA levels Increases glutathione peroxidase 4 levels Decreases the expression of cyclo-oxygenase 2	Relieves lipid oxidative stress	[103,104]
Omentin-1	Stimulates the Akt-endothelial NOS signaling pathway	Reduces oxidative stress Suppresses apoptosis	[105]
IL-6	Induces the expression of the proapoptotic protein Bax Suppresses the production of the TFAM protein	Promotes mitochondrial dysfunction	[106,107]

Abbreviations: Akt, protein kinase B; AMPK, AMP-activated protein kinase; ATF4, activating transcription factor 4; CHOP, CCAAT-enhancer-binding protein homologous protein; ERK1/2, extracellular signal–regulated kinase 1/2; GSH, glutathione; GST, glutathione-S-transferase; HNRNPA1, heterogeneous nuclear ribonucleoprotein A1; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MDA, malondialdehyde; NOS, nitric oxide synthase; NOX2, NADPH oxidase-2; Nrf2, nuclear factor erythroid 2–related factor 2; PGC-1β, peroxisome proliferator–activated receptor-gamma coactivator 1-beta; PI3K, phosphatidylinositol 3-kinase; SIRT1, Sirtuin; Smad3, small mother against decapentaplegic (SMAD) family member 3; SREBP-1c, sterol regulatory element-binding protein-1c; TFAM, mitochondrial transcription factor A; UCP2, uncoupling protein 2.

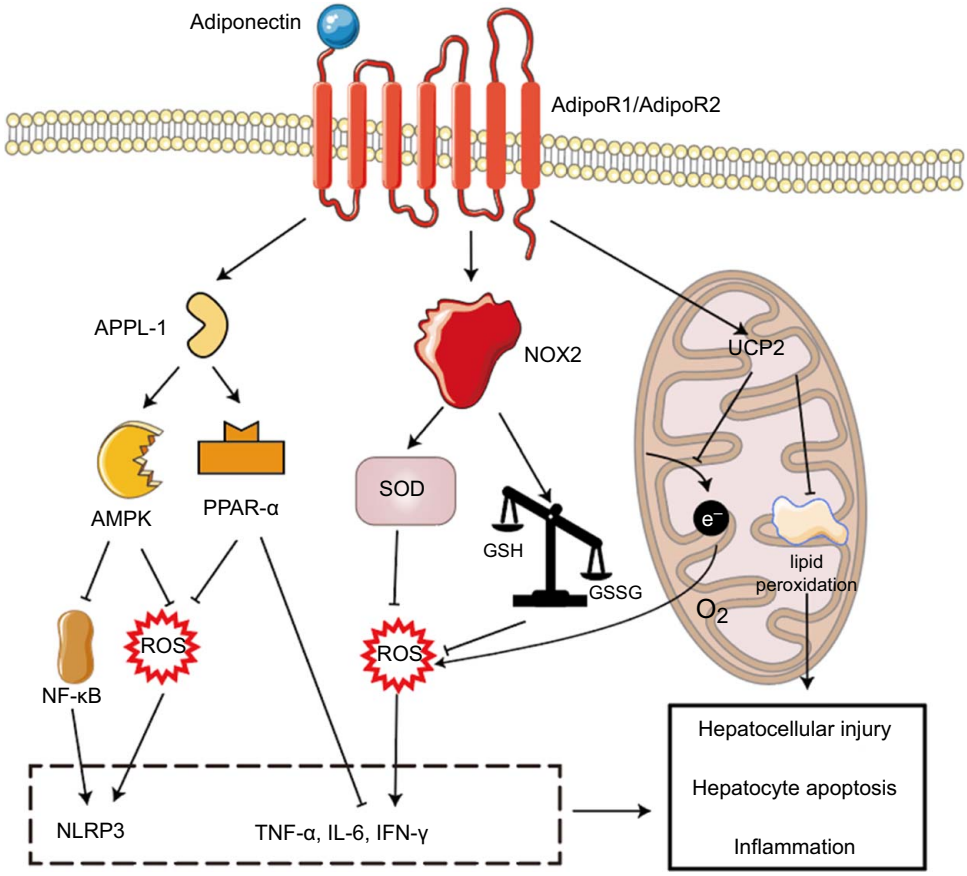


FIGURE 2 Molecular action of adiponectin in the liver. Mechanistic mechanism by which adiponectin attenuates deleterious inflammatory mechanisms, oxidative status, and lipid peroxidation simultaneously. Abbreviations: AdipoR, adiponectin receptor; AMPK, AMP-activated protein kinase; APPL, adaptor protein containing the pleckstrin homology domain, phosphotyrosine-binding domain and a leucine zipper motif; GSH, glutathione; GSSG, oxidized glutathione; IFN-γ, interferon-γ NLRP3, NLR family pyrin domain–containing 3; NOX2, NADPH oxidase-2; PPARα, peroxisome proliferator–activated receptor alpha; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; UCP2, uncoupling protein 2.

production.[111] Within the liver, leptin plays its role through the regulation of carbohydrate response element-binding proteins, effectively mitigating lipid accumulation while promoting lipid mobilization. Maintaining physiological levels of leptin is imperative for preventing hepatic steatosis.[112] However, as MASLD progresses, leptin can acquire proinflammatory and profibrotic functions.[113] In addition, leptin has oncogenic potential and stimulates the proliferation, invasion, and migration of HCC cell lines.[114]

In the context of hepatic steatosis, the presence of leptin in hepatic macrophages can induce peroxynitrite-mediated oxidative stress, culminating in the activation of KCs. Peroxynitrite formation initiates the generation of free radicals through leptin, tyrosine nitration, and KC activation. Oxidative stress–induced leptin-mediated CD8+CD57+ T cells may be pivotal players in the progression of MASH.[72]

Furthermore, the ability of leptin to promote steatosis development and MASH progression hinges on its association with hepatic iron metabolism. After leptin is overexpressed in ob/ob mice, leptin upregulates hepcidin, a central regulator of iron homeostasis, leading to a marked increase in the iron content in the liver. Elevated hepatic iron levels induce toxicity by increasing hydroxyl radical production and mediating oxidative stress, thereby causing tissue damage.[73] Consequently, leptin has the potential for a dual role in MASLD, potentially protecting against steatosis while exerting proinflammatory and profibrotic effects.

FGF21

FGF21 is a prominent endocrine regulatory factor that is synthesized primarily within the liver and adipose tissue; its importance lies in its capacity to ameliorate various critical hepatic disorders by orchestrating pivotal metabolic pathways.[115] FGF21 curbs lipid biosynthesis, promotes fatty acid β-oxidation, increases hepatic insulin sensitivity, curtails the influx of VLDL into the liver, and alleviates ER stress in the hepatic milieu (Figure 3).[116–118]

The hepatic expression of FGF21 is induced during ER stress, a process mediated by the PERK-eIF2α-

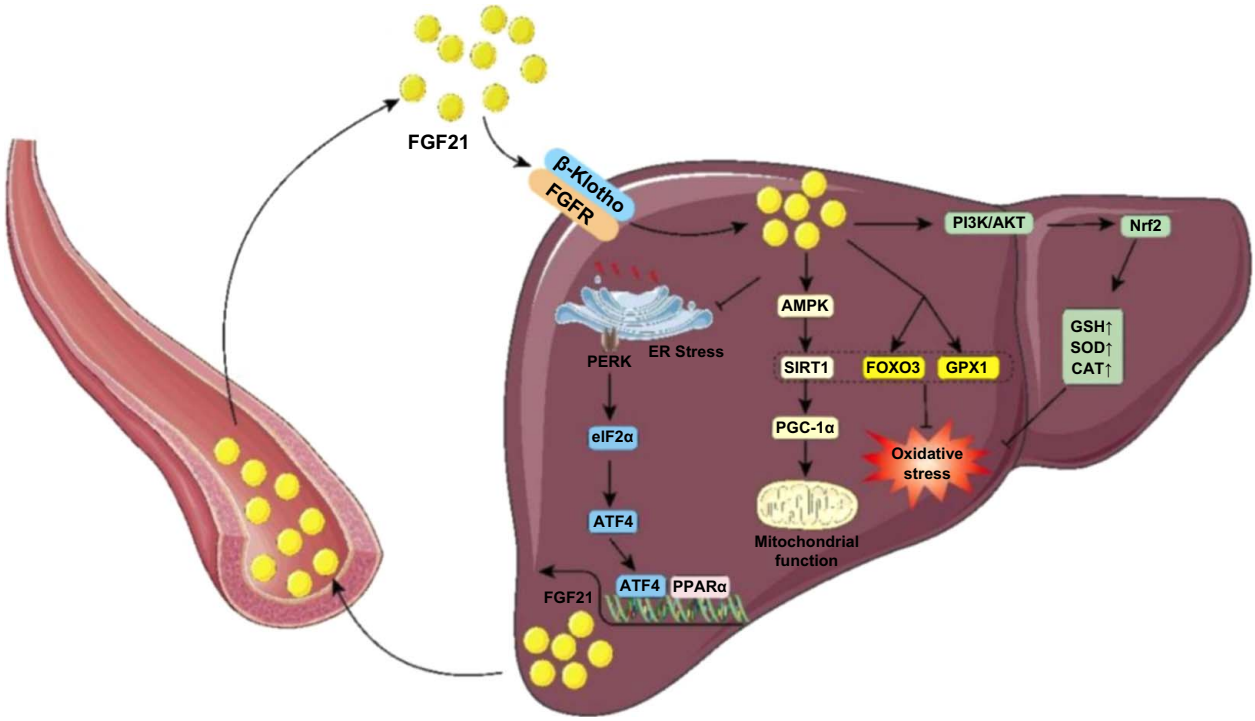


FIGURE 3 Mechanism of action of FGF21 in the liver. FGF21 can act on the liver through blood circulation. Moreover, the liver itself can secrete FGF21, which acts in an autocrine, paracrine, or endocrine manner. Abbreviations: AMPK, AMP-activated protein kinase; ATF4, activating transcription factor 4; Cat, catalase; eIF2α, eukaryotic initiation factor 2 alpha; ER, endoplasmic reticulum; FGFR, fibroblast growth factor receptor; FOXO3, forkhead box transcription factor 3; GPX1, glutathione peroxidase 1; GSH, glutathione; Nrf2, nuclear factor erythroid 2–related factor 2; PERK, PKR-like ER kinase; PGC-1α, proliferator–activated receptor-gamma coactivator 1-alpha; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; PPARα, peroxisome proliferator–activated receptor alpha; SIRT1, sirtuin 1; SOD, superoxide dismutase.

ATF4 pathway. Loss of FGF21 exacerbates ER stress–induced hepatic injury and TG accumulation.[119] Interestingly, through the eIF2α-ATF4 axis, which is triggered by the ER stress response, FGF21 serves as a compensatory mechanism that mitigates hepatic injury and counters hepatic lipid accumulation induced by ER stress.[120] FGF21 is the target gene of both ATF4 and CHOP.[121] FGF21 also forms a negative feedback loop to suppress the chronic activation of the ATF4/CHOP-mediated prosteatotic and proapoptotic pathways.[74]

FGF21 has been shown to activate the AMPK-sirtuin (SIRT1) pathway, thereby enhancing mitochondrial oxidative function and mitigating oxidative stress, which attenuates hepatic damage.[75] FGF21 increases antioxidant capacity and apoptosis through the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway and nuclear factor erythroid 2–related factor 2 (Nrf2)-mediated signaling, thus protecting against oxidative stress–induced hepatic damage in murine models.[76] Furthermore, FGF21 promotes PPARα-mediated transcriptional control over hepatic genes, with PPARα acting as a transcription factor activated by free fatty acids. Research suggests that, during the initial stages of oxidative stress, the liver increases FGF21 secretion to counterbalance fatty acid deposition, thereby shielding against ER stress and cellular damage resulting from obesity. These favorable metabolic effects are disrupted by the activation of the hepatic PPARα-FGF21 signaling axis, thereby promoting interorgan communication between the liver and adipose tissue.[77]

Adding another layer of complexity, FGF21 treatment results in increased transcription of genes associated with the oxidative stress response and antioxidants, such as superoxide dismutase 2 (SOD2), catalase (Cat), glutathione peroxidase 1 (GPX1), sirtuin, and forkhead box transcription factor 3 (FOXO3), in wild-type mice. This transcriptional shift is coupled with increased metabolism.[78] Notably, in another murine study, $Fgf21^{-/-}$ mice presented elevated expression of very low-density lipoprotein receptor (VLDLR) in hepatic tissues. However, the administration of recombinant human FGF21 effectively inhibited ER stress–induced VLDLR expression and diminished hepatic steatosis.[122]

Moreover, studies have revealed that FGF21 analogs have the potential to enhance mitochondrial function and adequately manage surplus fatty acids while preventing the generation of ROS, thereby reducing oxidative damage and lipid peroxidation.[123] Treatment with efruxifermin, a long-acting Fc–FGF21 fusion protein, for 12 weeks is associated with an obvious reduction in liver fat content. Consequently, efruxifermin rapidly decreases the levels of markers of

hepatic stress and damage, such as ALT, AST, and N-terminal type III collagen propeptide.[124] Furthermore, by bolstering fatty acid activation and mitochondrial β-oxidation in the liver, long-acting FGF21 PsTag600-FGF21 reverses hepatic steatosis in mice in a choline-deficient, high-fat diet–induced MASH mouse model.[79]

Retinol-binding protein 4

Retinol-binding protein 4 (RBP4) is a newly discovered adipokine that is secreted primarily by hepatic and adipose cells; it plays a key role in transporting retinol and thyroxine from the liver to peripheral tissues while counteracting lipotoxic damage induced by various stimuli.[125] A growing body of evidence suggests that elevated serum RBP4 levels are associated with an increased risk of metabolic diseases, including obesity, type 2 diabetes, and MASLD.[126–128] There have been few reports on the role of RBP4 in the context of HCC, and some clinical studies have shown a significant reduction in RBP4 levels in liver tissues from patients with HCC.[129,130]

Research has revealed that RBP4 significantly upregulates the expression of peroxisome proliferator–activated receptor-gamma coactivator 1-beta (PGC-1β) and SREBP-1c, ultimately promoting de novo lipogenesis.[80] In addition, investigations led by Liu and colleagues have shown that both circulating RBP4 levels and hepatic RBP4 expression are abnormally elevated in patients with MASLD and MASLD model mice. These elevated levels correlate positively with increased hepatic TG accumulation. RBP4 overexpression exacerbates hepatic mitochondrial dysfunction by decreasing oxidative capacity, thereby promoting hepatic steatosis in mice. Further studies have revealed that RBP4 impairs mitochondrial lipid oxidation by inhibiting sirtuin 3 (SIRT3)-dependent lysine deacetylation of long-chain acyl-CoA dehydrogenase (LCAD). In RBP4-overexpressing mice and HepG2 cells treated with RBP4, the acetylation levels of the LCAD protein significantly increase, resulting in compromised hepatic mitochondrial function, particularly fatty acid oxidation capacity, and reduced mitochondrial metabolic enzyme levels, thereby exacerbating hepatic steatosis.[81]

Moreover, studies have revealed that RBP4 is enriched in serum exosomes. Exosomal RBP4 significantly enhances the M1-like polarization of KCs by promoting the activation of NOX2 and NF-κB, in addition to the accumulation of ROS. This leads to the excessive production of inflammatory cytokines, including TNF-α. This excess of cytokines subsequently significantly increases intracellular free fatty acid uptake and the expression of genes associated with lipogenesis (FAS and SREBP-1c) in L02 cells treated with palmitic acid, whereas it reduces the expression of genes associated with fatty acid degradation (carnitine palmityl transferase I and PPARα). This process promotes de novo lipogenesis.[82]

Irisin

Irisin, a myokine that originates primarily from muscle cells, is generated through proteolytic cleavage of fibronectin type III domain–containing protein 5 (FNDC5), which possesses 5 transmembrane domains. This intriguing signaling molecule acts as a mediator, fostering communication between muscle and adipose tissue.[131] Notably, while muscle tissue is the principal source of irisin, emerging research posits that adipose tissue, in addition to muscle, can synthesize and secrete irisin, thus underscoring its dual role as both a myokine and an adipokine.[132] In various contexts, including in human liver cancer cells, primary human hepatic cells, and diabetic murine models, irisin has demonstrated the capacity to ameliorate hepatic gluconeogenesis and increase glycogen synthesis. These beneficial effects are orchestrated through the activation of key pathways, such as the PI3K/Akt and AMPK pathways, ultimately culminating in improved glucose homeostasis.[133] Intracellular iron overload can result in the production of excess amounts of ROS and induce the production of lipid peroxides, ultimately triggering ferroptosis. Moreover, irisin significantly reduces lipid peroxidation and iron overload, increases antioxidant capacity, and inhibits ferroptosis in type 1 diabetic mice through the eIF2α-ATF4-CHOP pathway.[83]

Moreover, pioneering investigations led by Park and colleagues revealed the ability of irisin to mitigate oxidative stress, which is typically induced by palmitic acid, in murine liver cells (AML12 cells) and primary epithelial cells. Irisin exerts inhibitory control over pivotal regulators of lipogenesis, including liver X receptor-alpha and SREBP-1c. This inhibitory effect effectively curtails lipid accumulation within hepatic cells.[84] Following exposure to hydrogen peroxide, AML12 hepatic cells exhibit an increase in ROS production, an effect that profoundly mitigates the effects of irisin. This phenomenon suggests that irisin plays a role in modulating oxidative homeostasis within the liver.[85]

Furthermore, evidence suggests that irisin, through the attenuation of ER stress, can prevent lipid accumulation in macrophages, thereby shielding these immune cells from apoptotic death. This finding underscores the potential of irisin as a regulator of pathways associated with ER stress.[134,135] Liao et al[86] reported that, by modulating the phosphorylation of PERK in murine liver tissue and ex vivo hematopoietic stem cells, irisin increases the stability of heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1) to alleviate ER stress and mitigate liver fibrosis.

In addition to its various beneficial effects, exogenous irisin significantly inhibits the expression of

mitochondrial fission-related proteins, namely, dynamin-related protein 1 (DRP1) and fission 1, in the context of hepatic ischemia/reperfusion (I/R) injury. Furthermore, exogenous irisin increases the mitochondrial number, elevates the expression of peroxisome proliferator–activated receptor-gamma coactivator 1-alpha (PGC-1α), and increases the expression of mitochondrial transcription factor A (TFAM). The role of irisin in curtailing oxidative stress is underscored by its ability to upregulate UCP2 expression during liver I/R injury. Collectively, these findings indicate that irisin mitigates hepatic I/R injury by suppressing mitochondrial fission, stimulating mitochondrial biogenesis, and ameliorating oxidative stress.[87]

Other adipokines

Chemerin, which is predominantly secreted by adipocytes and hepatocytes, functions as an adipokine; it acts as a ligand, binding to chemokine-like receptor 1 (CMKLR1), G-protein coupled receptor 1 (GPR1), and CC chemokine receptor–like 2 (CCRL2). This adipokine plays a pivotal role in various physiological processes, including adipogenesis, insulin signaling, and energy metabolism.[136,137] However, the role of chemerin in inflammation remains unclear, as it has been reported to exert both proinflammatory and anti-inflammatory effects in different models, probably due to the existence of different isoforms.[138] A previous study revealed that chemerin-overexpressing mice present lower hepatic oxidative stress, F4/80 and CC-chemokine ligand 2 (CCL2) protein expression, and mRNA expression of inflammatory genes than do control mice.[88] Another study revealed the potential of chemerin in ameliorating high-fat diet (HFD)-induced MASH. Chemerin significantly reduces serum ALT, AST, interleukin-1β (IL-1β), IL-6, and TNF-α levels; alleviates insulin resistance (IR) and leptin resistance (LR); and ameliorates hepatic pathology in MASH. Moreover, chemerin prevents increased oxidative stress in MASH model mice by regulating the antioxidant defense system (downregulating MDA expression and upregulating SOD expression), a process associated with chemerin/CMKLR1-mediated Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3) phosphorylation.[89]

Vaspin, an adipokine originating from visceral adipose tissue, is released by adipocytes, hepatocytes, and various other cells. Research indicates that vaspin effectively reduces hepatic fibrosis by activating AMPK through the 78-kDa glucose-regulated protein (GRP78) receptor and downregulating NF-κB gene expression.[139] Nakatsuka et al reported that vaspin binds to the cell surface receptor GRP78 and induces the phosphorylation of components of the Akt pathway, preventing metabolic dysfunction induced by ER stress. Owing to its anti-inflammatory properties, vaspin can reduce oxidative stress, increase insulin sensitivity, and serve as a compensatory factor in metabolic dysfunction.[90,91] In an HCC cell line, apoptosis was suppressed after vaspin treatment, and this effect was accompanied by high levels of ROS and low levels of nitric oxide and superoxide anions.[92]

Apelin, another adipose factor produced and secreted by adipocytes, is considered a crucial regulator of lipid metabolism. Mice lacking apelin exhibit increased obesity and elevated circulating free fatty acid levels. Treatment with apelin reduces hepatic steatosis in insulin-resistant mice by decreasing de novo lipogenesis.[93] Apelin-13 has been shown to improve glucose and lipid metabolism in mice with gestational diabetes mellitus through the PI3K/Akt pathway, reducing damage caused by oxidative stress and inflammation.[94] However, ectopic apelin expression in HCC cells promotes cell proliferation, accelerates G1/S progression, and inhibits apoptosis.[140] The above studies indicate that apelin plays different roles in different stages of MASLD.

Resistin, which is predominantly secreted by adipose tissue, inflammatory cells such as macrophages and monocytes, and HSCs, functions as a cytokine and activates the NF-κB signaling pathway, thereby promoting the synthesis of proinflammatory factors such as TNF-α and IL-6.[95] Clinical investigations have revealed a correlation between heightened resistin expression and the severity of hepatic inflammation and fibrosis in individuals with MASH.[141] In animal studies, resistin has been shown to hinder the phosphorylation of 5′ adenosine monophosphate–activated protein kinase α in mice fed a high-fat diet. This exacerbates hepatic lipid accumulation induced by ER stress and mitochondrial damage.[96] In human monocytes, resistin mRNA expression is positively associated with the mRNAs expression of the ER stress markers immunoglobulin heavy chain-binding protein (BiP) and CHOP. Tunicamycin increases resistin mRNA expression through the PERK-ATF4-CHOP pathway in THP-1 human monocytes.[97]

Visfatin, which is generated primarily by visceral adipose tissue, is an adipocytokine with dual proinflammatory and insulin-mimetic properties; it plays a crucial role in systemic glucose and lipid metabolism.[142] Visfatin influences various pathways, including oxidative stress response, cell apoptosis, lipid and glucose metabolism, insulin resistance, and inflammation. The involvement of visfatin in these pathways potentially contributes to the pathogenesis of MASLD.[143] Visfatin induces proinflammatory cytokine production and inhibits insulin signaling through the STAT3 and NF-κB pathways in HepG2 cells.[98] In a murine model of MASH induced by a methionine-choline–deficient diet, visfatin increased ER stress and elevated levels of ROS. Furthermore, the JNK signaling

pathway was activated, and the liver displayed increased inflammatory cell infiltration, proinflammatory cytokine levels, and fibrotic marker expression.[99]

Insulin-like growth factor 1 (IGF-1) is produced mainly by the liver, but almost all tissues are able to secrete IGF-1 for autocrine/paracrine function.[100] Pituitary growth hormone (GH) and liver-derived IGF-1 establish a negative feedback loop, and evidence exists that this negative feedback loop plays a unique role in MASLD.[144] Mitochondria are among the main intracellular targets of IGF-1, and some studies have shown that IGF-1 reduces oxidative stress in the liver and improves mitochondrial function.[100] IGF-1 normalizes mitochondrial function by increasing the membrane potential and ATPase activity and reducing intramitochondrial free radical production. In addition, IGF-1 reduces the expression of the active peptide of caspase 3 and reduces apoptosis.[101] In addition, GH-deficient rats present impaired mitochondrial morphology in hepatocytes, which can be alleviated by IGF-1 administration.[145] Castilla-Cortazar et al[102] reported that IGF-1 promotes the recovery of the mitochondrial transmembrane potential (MTP) and mitochondrial protein content to normal levels. It seems that IGF-1 can stimulate mitochondrial protein synthesis and improve mitochondrial function. In CCl4-induced cirrhosis, low-dose IGF-1 decreases lipid peroxidation, improves hepatic function, and reduces collagen deposition. Another study revealed that iron and copper play important roles in oxidative mechanisms, producing deleterious hydroxyl radicals that peroxidize lipid membranes and damage DNA. Myeloperoxidase (MPO) and nitric oxide are known sources of free radicals. Compared with control rats, untreated cirrhotic rats present increased hepatic levels of iron, ferritin, transferrin, copper, MPO, and inducible nitric oxide synthase (NOS). IGF treatment significantly reduces all these parameters.[146]

Adipsin, a secreted adipokine, plays an important role in preserving beta cells by controlling the complement pathway and generating C3a (an active form of complement component 3, C3) in diabetic mice and is associated with protection from type 2 diabetes in humans.[147] However, studies on the association between adipsin levels and MASLD are limited. A cross-sectional study revealed that circulating adipsin levels in obese Chinese adults are negatively associated with the risk of MASLD.[148] According to a recent study, higher mRNA adipsin levels are associated with reduced CHOP mRNA levels and elevated PPAR-gamma mRNA levels in WAT.[103] In addition, adipsin-overexpressing exosomes derived from pericardial adipose tissues alleviate iron overload in cardiac tissues. Adipsin also relieves lipid oxidative stress, as evidenced by decreased expression of cyclo-oxygenase 2 and increased glutathione peroxidase 4 levels.[104]

Omentin-1 (also known as intelectin-1) has been identified as a major visceral (omental) fat-secreted adipokine. Previous studies have shown that omentin-1 exerts anti-inflammatory effects and plays a crucial role in the regulation of apoptosis.[149,150] A meta-analysis demonstrated that circulating omentin levels were significantly lower in patients with MASLD than in healthy controls.[151] Salvoza et al[152] reported that omentin-1 significantly reduces TNF-α levels, ER stress, and oxidative stress in ex vivo VAT explants from obese patients and in fat-laden human hepatocytes in vitro. Another study revealed that omentin-1 promotes angiogenesis, inhibits oxidative stress, and reduces apoptosis by stimulating the Akt-endothelial NOS signaling pathway in response to ischemia in vitro.[105]

IL-6 is released from visceral adipocytes into the portal vein, where it is shunted directly into the liver.[50] Prolonged exposure to IL-6 is associated with the activation of the mitochondrion-destabilizing proapoptotic protein Bax. The activation of Bax sensitizes hepatocytes to the intrinsic apoptosis pathway by tipping the balance between anti-apoptotic and proapoptotic signals toward mitochondrial destabilization and death through increased caspase-9 activation.[106] A study revealed that IL-6 suppresses the production of the TFAM protein, which is a multifunctional DNA-binding protein required for mtDNA transcription and organization. Mitochondria adapt to oxidative stress through the regulation of division/fusion and optimization of mtDNA matrix processes and biogenesis. Impairment of mitochondrial adaptation contributes to lipid deposition and ROS accumulation.[107]

CONCLUSIONS

In conclusion, adipokines play a pivotal role in the regulation of hepatic lipid metabolism, and disturbances in adipokine secretion can play a crucial role in the progression of metabolic disorders. Variations in nutritional status, including excessive caloric intake, high-fat diet consumption, and physical inactivity, influence the production and secretion of adipokines within adipose tissues. These alterations subsequently regulate a multitude of metabolic and immune pathways, ultimately promoting or exacerbating the disruption of metabolic homeostasis. The impact of alterations in adipokine levels extends beyond the modulation of lipid metabolism. Adipokines also influence insulin sensitivity, appetite regulation, and the accumulation of hepatic lipids. Furthermore, these molecules are intricately involved in various deleterious processes, including the modulation of inflammatory markers, oxidative stress, and the perturbation of mitochondrial function. Dysregulation of adipokines has emerged as a pivotal driving force behind the progression of MASLD and its progression to MASH.

The development of MASH is a critical transitional step in the clinical progression of MASLD, and pharmacological interventions specifically targeting MASH remain limited. This comprehensive review focused on previously identified adipokines and associated pathways as well as emerging adipokines. This review was conducted to aid the discovery of novel targets for diagnosing and treating MASLD/MASH. These adipokines have potential as markers of disease progression in MASLD or even as early markers for HCC development in this setting. The manipulation of adipokine levels and the development of pharmaceutical agents targeting adipokines and their corresponding receptors represent tangible approaches to decrease hepatic insulin resistance, mitigate hepatic steatosis, and alleviate oxidative stress. These innovative strategies may guide the development of novel therapeutic approaches for MASLD/MASH treatment.

AUTHOR CONTRIBUTIONS

Ke Zhao: writing—original draft, and writing—review and editing. Heng Zhang: writing—original draft and software. Wenyu Ding: resources and supervision. Xiaoshuai Yu: software and visualization. Yanli Hou: investigation. Xihong Liu: methodology. Xinhua Li: conceptualization and funding acquisition. Xiaolei Wang: conceptualization, funding acquisition, and writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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