

Mitochondrial dysfunction in metabolic dysfunction-associated steatotic liver disease: Mechanistic insights and therapeutic horizons (Review)

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Abstract. Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a central driver of the global chronic liver disease burden. Its progression toward metabolic dysfunction-associated steatohepatitis and advanced liver fibrosis is shifting from the traditional view of simple lipid accumulation to a dynamic pathogenic network centered on mitochondrial dysfunction. The present review systematically delineates the non-linear kinetic evolution of mitochondrial alteration from early 'hormetic compensatory adaptation' to late 'bioenergetic collapse' during MASLD progression. The molecular basis of mitochondrial quality control, including fission/fusion dynamics, mitophagy, the mitochondrial unfolded protein response and inter-organelle cross-talk via mitochondria-associated endoplasmic reticulum membranes are critically discussed. Focus is placed on the key homeostatic networks regulated by the sirtuin family (SIRT1-SIRT7), dissecting their context-dependent roles and current academic controversies. Finally, contemporary clinical and preclinical therapeutic strategies targeting mitochondrial metabolism are evaluated, providing a strict evidence-graded translational perspective from basic research toward clinical precision medicine.

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1. Introduction and nomenclature evolution

With the global pandemic of obesity and type 2 diabetes (T2D), the epidemiological spectrum of chronic liver disease has undergone profound changes (1,2). To more accurately reflect the underlying metabolic pathophysiology, international consensus has updated the nomenclature from non-alcoholic fatty liver disease to metabolic dysfunction-associated steatotic liver disease (MASLD) and from non-alcoholic steatohepatitis (NASH) to metabolic dysfunction-associated steatohepatitis (MASH) (3-5).

This diagnostic transition represents more than a semantic revision; it shifts the translational research paradigm from an exclusionary diagnosis to an inclusionary, metabolic-centric framework. Clinically, this refinement anchors hepatic pathology to cardiometabolic risk factors, including central obesity, hyperglycemia, dyslipidemia and hypertension (1,3,4). Age, obesity, insulin resistance and T2D are associated with advanced fibrosis, whereas elevated ferritin in NAFLD may reflect hepatic iron burden and should not be interpreted as an independent fibrosis determinant in isolation (6-8). In translational research, adopting the MASLD framework encourages preclinical models to reproduce the systemic metabolic context of human disease; nevertheless, predictive validity still depends on how closely an individual model recapitulates the relevant human phenotype.

Clinically, the pathology advances sequentially from a healthy liver to MASLD with simple steatosis, MASH, progressive liver fibrosis (stages F1-F3 according to the NASH

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Clinical Research Network [NASH CRN] fibrosis staging system) and cirrhosis (stage F4) (9). This disease follows a pathological cascade that may culminate in cirrhosis and hepatocellular carcinoma (6) (Fig. 1). Under physiological conditions, the liver fine-tunes systemic lipid homeostasis by balancing fatty acid uptake, de novo lipogenesis (DNL), β -oxidation and very-low-density lipoprotein secretion (10,11). Chronic nutrient overload and insulin resistance disrupt this balance, increase DNL and promote hepatic lipid accumulation (11,12). Hepatic steatosis is conventionally defined by steatosis affecting >5% of hepatocytes or an equivalent increase in liver fat content, rather than by >5% triglycerides within individual hepatocytes (3,6).

Hepatic lipid accumulation is not an isolated event; mitochondria lie at the intersection of nutrient overload, lipid-droplet handling and progressive cellular injury (13–15). Notably, mitochondria are not merely passive recipients of lipotoxicity; instead, their functional phenotype can shift from early compensatory adaptation to late decompensated failure during MASLD progression. Consequently, the present review tracks the evolution of mitochondrial dysfunction, details the molecular cross-talk driving liver injury, and evaluates epigenetic and metabolic regulation by the sirtuin family to identify clinically relevant therapeutic opportunities.

2. Mitochondrial dysfunction: The core hub driving MASLD to MASH progression

Hepatic mitochondrial physiology and lipid homeostasis. Mitochondria serve as the central hub for regulating systemic lipid homeostasis. Under physiological conditions, cytosolic free fatty acids (FFAs) strictly rely on the carnitine shuttle system to enter the mitochondrial matrix. This system is coordinately assembled by long-chain acyl-CoA synthetase on the mitochondrial outer membrane, carnitine palmitoyltransferase 1 (CPT1), carnitine-acylcarnitine translocase and CPT2 within the mitochondrial matrix (16,17).

Upon entering the matrix, fatty acids undergo β -oxidation. The NADH and FADH₂ generated by this pathway deliver high-energy electrons into the electronic transport chain (ETC) (18). While consuming 1–2% of oxygen to generate physiological free radicals, the ETC establishes a proton gradient across the inner mitochondrial membrane (IMM), forming an electrochemical transmembrane potential that ultimately drives ATP synthase to generate energy and regenerates the NAD⁺ and FAD required for subsequent oxidation cycles (19).

Biphase adaptive mechanism: Evolution from compensatory overload to bioenergetic failure. Mitochondrial involvement in MASLD does not follow a simple, linear progressive decline; rather, it exhibits a distinct non-linear biphase kinetic curve characterized by early functional hypermetabolism followed by late bioenergetic exhaustion.

Early hormetic compensatory adaptation phase (mitohormesis). In the initial stages of simple steatosis, systemic insulin resistance in peripheral adipose tissue drives unrestrained lipolysis and increases the influx of circulating free fatty acids into the liver. Hepatic mitochondria can initially respond by increasing substrate oxidation, tricarboxylic acid (TCA) cycle

flux and respiratory activity; in humans with simple steatosis, this compensatory increase is lost after progression to steatohepatitis, while diet-induced models likewise demonstrate elevated TCA cycle activity during fatty liver development (20,21). This adaptation may transiently preserve energy production but also increases reducing-equivalent delivery to the electron transport chain and can heighten oxidative pressure. Ketogenesis and related oxidative pathways provide additional outlets for acetyl-CoA, although whether these responses remain protective depends on disease stage and metabolic context (14,15).

Transition point and late bioenergetic collapse phase. When nutrient overload becomes chronic and exceeds mitochondrial homeostatic capacity, sustained substrate pressure uncouples TCA cycle activity from efficient oxidative phosphorylation, increases mitochondrial reactive oxygen species (mROS) and reduces ATP production. Insulin resistance also sustains hepatic DNL, further increasing the lipid burden (11,12). Hepatic PGC-1 α expression and activity can become impaired during MASH, and experimental loss of hepatic PGC-1 α reduces mitochondrial respiration and promotes inflammation and fibrosis (22,23). In parallel, incomplete lipid disposal favors the accumulation of diacylglycerols and ceramides that interfere with insulin signaling and cellular homeostasis (24,25). The resulting lipotoxic and oxidative injury can impair membrane integrity, promote hepatocyte ballooning and cell death, and release damage-associated signals and lipid-peroxidation products that activate hepatic stellate cells (HSCs) and accelerate fibrosis.

Oxidative stress outbreak and collapse of endogenous antioxidant defenses. Uncontrolled oxidative stress is a core mediator of hepatocyte injury, inflammation and fibrosis (26,27). Under physiological conditions, ETC complexes I and III exhibit only minor leaking of electrons (28). However, in the lipotoxic environment of MASH, this electron leakage worsens notably (29).

The continuous influx of saturated fatty acids alters mitochondrial membrane composition and increases lipotoxic stress. Ceramide accumulation and VDAC1-associated mitochondrial dysfunction have both been implicated in fatty liver pathology, while experimental targeting of VDAC1 attenuates steatosis and NASH-associated injury in mice (25,30,31) (Fig. 2). These findings support a role for VDAC1 in mitochondrial injury but do not establish that free fatty acids directly alter VDAC voltage gating in human MASH.

This lipotoxic mROS burden can overwhelm endogenous antioxidant defenses, including SOD2, glutathione-dependent systems, catalase and thioredoxin/peroxiredoxin pathways, thereby permitting lipid peroxidation and the accumulation of cytotoxic aldehydes such as 4-hydroxy-2-nonenal and malondialdehyde (32,33). Oxidative injury also extends to nuclear and mitochondrial DNA; mitochondrial DNA damage and cytochrome b variation have been associated with fatty liver disease severity (34).

At the signaling level, ROS-responsive JNK can interact with the mitochondrial scaffold protein Sab, inhibit mitochondrial respiration and promote cell death (35). Mitochondrial c-Src independently regulates phosphorylation of respiratory-chain components and cell survival, although the available evidence does not establish a direct chronic JNK-to-c-Src inhibitory

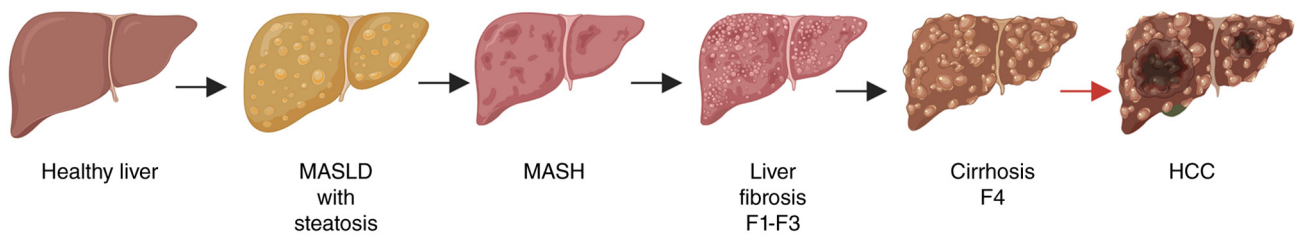


Figure 1. Progression of MASLD. Schematic representation showing the clinical continuum of fatty liver disease progression. The pathology advances sequentially from a healthy liver to MASLD with simple steatosis, MASH, progressive liver fibrosis [stages F1-F3 according to the NASH Clinical Research Network (NASH CRN) fibrosis staging system] and cirrhosis (stage F4). Final progression can lead to HCC. MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma.

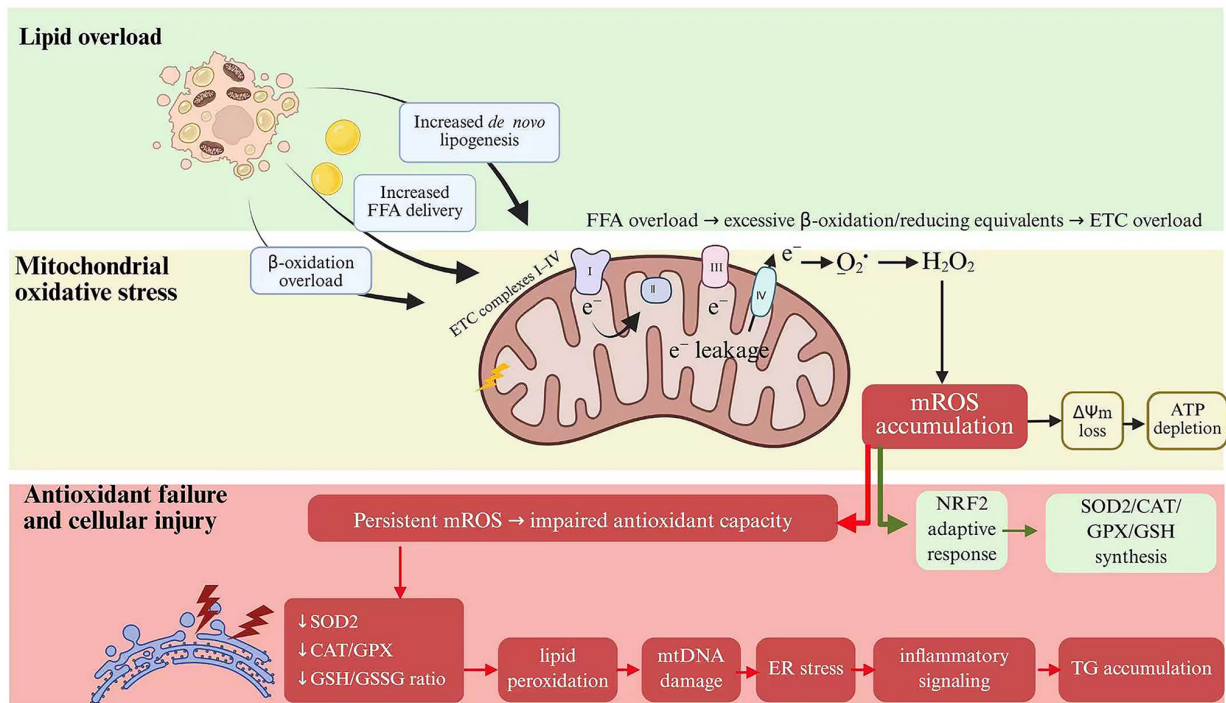


Figure 2. Evidence-bounded model of lipid-induced mitochondrial oxidative stress and cellular injury. Nutrient overload and insulin resistance increase hepatic DNL and lipid burden (10,11), while ceramides and VDAC1-associated dysfunction contribute to mitochondrial injury (24,29,30). Excess mROS can overwhelm antioxidant systems, promote lipid peroxidation and damage mitochondrial DNA (31-33); ROS-responsive JNK-Sab signaling can further impair respiration and promote cell death (34). The sequence is a conceptual framework and does not establish a universal linear NRF2-to-antioxidant-exhaustion pathway in human MASH. DNL, *de novo* lipogenesis; VDAC1, voltage-dependent anion channel 1; mROS, mitochondrial reactive oxygen species; JNK, c-Jun N-terminal kinase; Sab, SH3 domain-binding protein 5; mtDNA, mitochondrial DNA.

pathway in MASH (36). Redox-sensitive signaling in HSCs contributes to their activation and extracellular matrix deposition (37,38). In parallel, mitochondria-associated non-coding RNAs can regulate mROS output: Downregulation of the mitochondria-localized circRNA SCAR promotes inflammatory signaling in NASH, and broader evidence implicates lncRNAs and circRNAs in NAFLD pathobiology (39,40).

Structural quality control and organelle cross-talk

Mitochondrial dynamics imbalance: From network fusion to fragmented collapse. Mitochondrial morphology depends on a dynamic balance between fusion, which mixes mitochondrial contents, and fission, which segregates damaged regions for clearance. NAFLD models show excessive fragmentation and altered DRP1-dependent fission, and experimental reduction of mitochondrial fission alleviates hepatic steatosis (41,42).

However, the currently cited evidence does not establish DRP1 Ser616 phosphorylation as a universal initiating event in human MASH.

The fusion and turnover machinery is also impaired during fatty liver progression. Experimental and clinical studies report altered mitofusin expression, disturbed mitochondrial dynamics and reduced markers of mitochondrial turnover in NAFLD (42,43). At the inner mitochondrial membrane, cellular stress activates the metalloprotease OMA1, which cleaves long-form OPA1 and thereby remodels inner-membrane fusion and cristae organization (44).

Mitophagy impairment and mitochondrial unfolded protein response (UPR^{mt}) dysregulation: From quality control to apoptotic switch. Mitochondrial quality control integrates fusion, lipid droplet-mitochondria communication and selective

organelle turnover. In liver models, MFN2-dependent contacts promote fatty acid oxidation, BNIP3 regulates mitochondrial function and lipid metabolism, and ALCAT1 links defective mitophagy to steatosis (45-47). These data support impaired mitochondrial quality control in fatty liver disease but do not justify a universal model in which advanced MASH is caused specifically by defective proteasomal degradation of PINK1.

To survive mitochondrial proteotoxic stress, cells activate the UPR_{mt}. Accumulation of misfolded mitochondrial proteins engages proteases and retrograde signaling, and the transcription factor ATF5 is required for a mammalian UPR_{mt} program that induces nuclear-encoded mitochondrial chaperones and other protective genes (48,49).

Under persistent lipotoxic stress, however, UPR_{mt} signaling may become insufficient or maladaptive. Reviews of UPR_{mt} biology and fatty liver disease describe a context-dependent transition from compensatory proteostasis toward integrated stress signaling and cell-death pathways involving ATF4 and CCAAT/enhancer-binding protein homologous protein (CHOP) (49-51). The precise contribution of CHOP-dependent Bcl-2 and Bax/Bak regulation to human MASH remains less directly established than the broader stress-response framework.

Mitochondria-associated endoplasmic reticulum (ER) membranes (MAMs) and cellular calcium homeostasis dysregulation. Mitochondria establish tight bidirectional communication bridges with the ER via specialized contact sites known as MAMs (52). MAMs serve as specialized subcellular channels for the direct transfer of Ca²⁺ and structural lipids between the two organelles (53).

In obesity-associated liver, endoplasmic reticulum-mitochondria contacts are reorganized and can become chronically enriched, causing mitochondrial Ca²⁺ overload, impaired oxidative capacity and oxidative stress (54). MAMs also adapt dynamically to nutrient and glucose availability and regulate hepatic mitochondrial metabolism. Thus, MAM remodeling rather than uniform hyper-formation is the more defensible disease model. Excessive calcium transfer can predispose mitochondria to permeability transition and cell-death signaling, but the direction and magnitude of MAM remodeling are context-dependent and should not be generalized across all stages of MASH (55,56).

3. Sirtuin epigenetic metabolic network and mitochondrial homeostasis regulation

The sirtuin family (SIRT1-SIRT7) comprises NAD⁺-dependent deacetylases and deacylases whose activity is coupled to intracellular NAD⁺ availability. CD38 can drive NAD⁺ decline and SIRT3-dependent mitochondrial dysfunction in age-related metabolic settings, whereas enhancement of *de novo* NAD⁺ synthesis improves mitochondrial function in experimental models (57,58). These findings make NAD⁺ depletion a plausible modifier of the sirtuin network in MASH, although direct evidence that chronic hepatic inflammation universally causes CD38-mediated NAD⁺ collapse remains incomplete. A comprehensive overview of sirtuin localization, targets and disease-related roles is summarized in Table I.

Classical metabolic protective axis (SIRT1/2/3). SIRT1 supports hepatic mitochondrial metabolism through PGC-1 α deacetylation and improved fatty acid oxidation, and SIRT1-dependent autophagy protects hepatocytes from palmitate-induced lipotoxicity (59,60) (Fig. 3). The available studies support PGC-1 α regulation and autophagy induction but do not establish that ATG5 and ATG7 are both the direct hepatic substrates responsible for mitophagy in MASH.

SIRT2 can restrain inflammatory and lipogenic signaling through distinct substrates. SIRT2-dependent deacetylation regulates NLRP3 inflammasome activation in metabolic inflammation (61), while direct deacetylation of ATP-citrate lyase at K540, K546 and K554 destabilizes the enzyme and reduces hepatic lipid accumulation (62).

SIRT3 is a major regulator of mitochondrial redox homeostasis. It deacetylates isocitrate dehydrogenase 2 and regulates the mitochondrial redox state (63); in hepatocytes, the SIRT3-SOD2 axis influences susceptibility to lipotoxicity and autophagic responses (64) (Fig. 4). These studies support redox and stress-response functions but do not directly demonstrate that SIRT3 preserves cristae architecture or that LCAD activation accounts for all of its effects in MASH.

Context-dependent isoforms (SIRT4/7). SIRT4 can suppress fatty acid oxidation by deacetylating and inhibiting malonyl-CoA decarboxylase, thereby favoring malonyl-CoA accumulation and lipid anabolism (65). Conversely, SIRT4 has an anti-fibrotic role in HSCs, and miR-130b-5p-mediated suppression of SIRT4 promotes HSC activation and liver fibrosis (66). These findings indicate that the net effect of SIRT4 depends on substrate metabolism, cell type and disease stage rather than on degradation of the mitochondrial trifunctional protein- α subunit.

SIRT7 also has context-dependent nuclear and mitochondrial stress-response functions. SIRT7-dependent deacetylation of DDB1 regulates the lipogenic nuclear receptor TR4 and thereby influences hepatic lipid metabolism (67). In a distinct stem-cell system, SIRT7 participates in an NRF1-associated mitochondrial UPR metabolic checkpoint, linking nuclear transcriptional control to mitochondrial proteostasis (68). The latter mechanism provides a conceptual framework but should not be presented as direct evidence for SIRT7-GABP- β signaling in hepatocytes or MASH.

Epigenetic and non-acetylation modifications (SIRT5/6). SIRT5 removes succinyl and other acyl modifications from mitochondrial proteins. Proteomic and biochemical studies identify SIRT5-dependent desuccinylation across diverse metabolic pathways, including mitochondrial energy metabolism (69,70). However, the cited studies are not direct evidence that CPT1A and succinate dehydrogenase are the defining SIRT5 targets in human MASH.

SIRT6 restrains hepatic lipogenesis. Experimental studies show that SIRT6 suppresses the LXR, ChREBP and SREBP1 lipogenic programs, while USP10 stabilizes SIRT6 and protects against hepatic steatosis, insulin resistance and inflammation (71,72) (Fig. 5). These data directly support SIRT6-dependent transcriptional control of lipid metabolism without requiring an unverified claim that promoter-specific H3K9 and H3K56 deacetylation explains the entire phenotype.

Table I. Comprehensive landscape of sirtuins (SIRT1-SIRT7) in MASLD/MASH pathophysiology.

Isoform	Subcellular localization	Key molecular targets	Expression profile in MASLD	Core mechanistic role	Translational/therapeutic potential	Academic controversies and context dependencies	(Refs.)
SIRT1	Nucleus/cytoplasm	PGC-1 α and autophagy-associated pathways	Frequently reduced in metabolic liver disease models	Supports fatty acid oxidation and hepatocyte autophagy; restrains lipotoxicity.	Potential target; direct MASH efficacy remains to be established.	Effects depend on NAD ⁺ availability, nutritional state and experimental context.	(58,59)
SIRT2	Cytoplasm	ACLY and NLRP3	Context- and stage-dependent	Destabilizes ACLY through deacetylation and modulates inflammation activity.	Preclinical; liver-selective modulation is required.	Inflammatory and hepatocyte-autonomous metabolic effects may differ by model.	(60,61)
SIRT3	Mitochondrial matrix	IDH2 and SOD2-associated redox pathways	Often reduced in lipotoxic liver models	Regulates mitochondrial redox homeostasis and hepatocyte susceptibility to lipotoxicity and autophagic stress.	Preclinical; no selective activator has established clinical efficacy in MASH.	The cited studies do not establish LCAD activation or cristae preservation as universal MASH mechanisms.	(62,63)
SIRT4	Mitochondrial matrix	MCD; miR-1-30b-5p-associated HSC pathways	Variable by cell type and disease stage	Suppresses fatty acid oxidation through MCD inhibition but can restrain HSC activation and fibrosis.	Emerging, context-dependent target.	Metabolic and fibrotic phenotypes can point in opposite directions across cell types.	(64,65)
SIRT5	Mitochondrial matrix	Broad mitochondrial succinylated and other acylated proteins	Context-dependent	Removes succinyl and related acyl modifications across multiple metabolic pathways.	Discovery/preclinical stage.	The cited evidence does not identify CPT1A or SDHA as defining targets in human MASH.	(68,69)
SIRT6	Nucleus	LXR, ChREBP, SREBP1 and USP10-associated regulation	Reduced in experimental steatotic liver	Restraints hepatic lipogenic transcription and protects against steatosis, insulin resistance and inflammation.	Preclinical therapeutic rationale.	Promoter-specific histone mechanisms do not explain the entire phenotype.	(70,71)
SIRT7	Nucleus/nucleolus	DDB1/TR4; NRF1-associated UPRmt in a distinct cell system	Variable/context-dependent	Regulates hepatic lipid metabolism through DDB1-TR4; also participates in a mitochondrial stress checkpoint outside hepatocyte/MASH models.	Controversial, context-dependent target.	NRF1-linked UPRmt evidence should not be recast as direct SIRT7-GABP- β signaling in MASH.	(66,67)

MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; PGC-1 α , peroxisome proliferator-activated receptor γ coactivator 1- α ; SREBP-1c, sterol regulatory element-binding protein 1c; ACLY, ATP citrate lyase; NLRP3, NLR family pyrin domain containing 3; IDH2, isocitrate dehydrogenase 2; SOD2, superoxide dismutase 2; MCD, malonyl-CoA decarboxylase; HSC, hepatic stellate cell; LXR, liver X receptor; ChREBP, carbohydrate-responsive element-binding protein; TR4, testicular receptor 4; UPRmt, mitochondrial unfolded protein response.

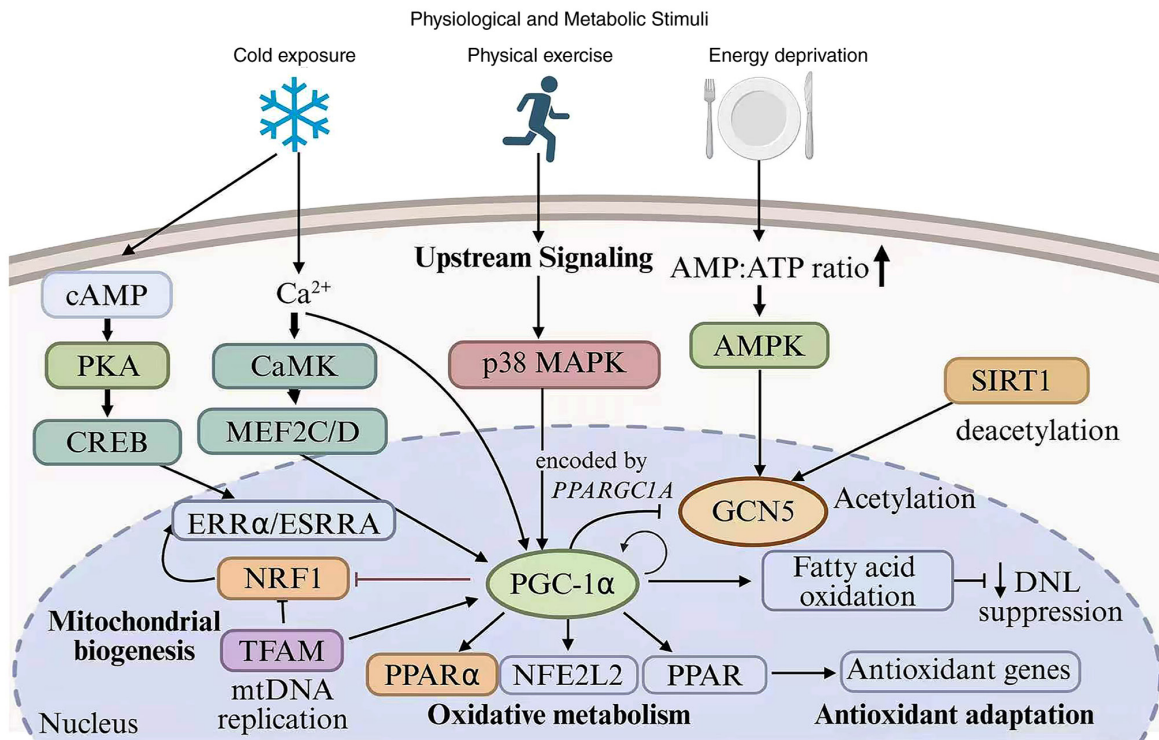


Figure 3. Evidence-bounded framework for PGC-1 α regulation and mitochondrial gene expression. Hepatic PGC-1 α supports mitochondrial respiration and lipid handling, and its experimental loss promotes inflammation and fibrosis (21,22). SIRT1-mediated PGC-1 α deacetylation improves fatty acid oxidation in a metabolic liver model (58). Other depicted upstream and downstream nodes represent a broader conceptual regulatory network and should not be interpreted as individually validated mechanisms in human MASH without pathway-specific evidence. PGC-1 α , peroxisome proliferator-activated receptor γ coactivator 1- α ; SIRT1, sirtuin 1; DNL, *de novo* lipogenesis; NRF1, nuclear respiratory factor 1; TFAM, mitochondrial transcription factor A.

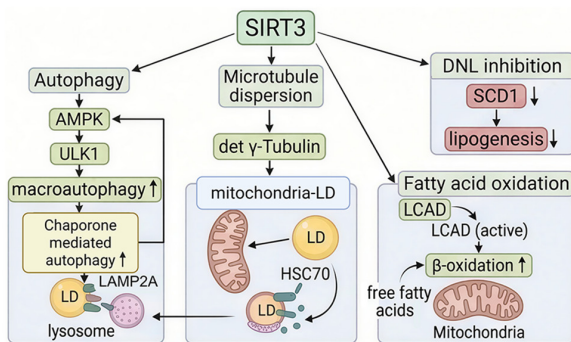


Figure 4. Evidence-bounded summary of SIRT3-linked redox and stress-response regulation in hepatocytes. SIRT3 deacetylates IDH2 and regulates the mitochondrial redox state, while the hepatocyte SIRT3-SOD2 axis influences susceptibility to lipotoxicity and autophagic responses (62,63). Downstream routes involving AMPK-ULK1, LAMP2A/HSC70, lipid droplet-mitochondria contacts or LCAD should be regarded as context-dependent hypotheses rather than mechanisms directly established by the cited MASH studies. IDH2, isocitrate dehydrogenase 2; SOD2, superoxide dismutase 2; AMPK, adenosine monophosphate-activated protein kinase; ULK1, Unc-51 like autophagy activating kinase 1; LAMP2A, lysosome-associated membrane protein type 2A; HSC70, heat shock cognate 71-kDa protein; LCAD, long-chain acyl-CoA dehydrogenase.

4. Therapeutic interventions targeting mitochondrial dysfunction and advanced metabolism

The drug development paradigm for MASLD has undergone a profound shift: From early ‘peripheral empirical antioxidant’ to modern ‘precise energy metabolic remodeling’. To provide

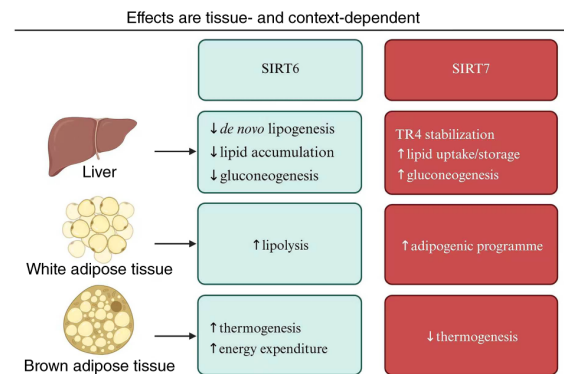


Figure 5. Hepatic and context-dependent metabolic functions of SIRT6 and SIRT7. In experimental liver systems, SIRT6 suppresses LXR-, ChREBP- and SREBP1-associated lipogenic programs, and USP10-dependent stabilization of SIRT6 protects against steatosis, insulin resistance and inflammation (70,71). SIRT7-dependent DDB1 deacetylation regulates TR4 and hepatic lipid metabolism (66), whereas its NRF1-associated mitochondrial-stress checkpoint was demonstrated in a distinct stem-cell system (67). Additional tissue-specific branches depicted in the schematic are contextual and should not be presented as direct evidence in hepatocytes or MASH. SIRT, sirtuin; LXR, liver X receptor; ChREBP, carbohydrate-responsive element-binding protein; SREBP1, sterol regulatory element-binding protein 1; USP10, ubiquitin-specific peptidase 10; DDB1, damage-specific DNA-binding protein 1; TR4, testicular receptor 4; NRF1, nuclear respiratory factor 1.

a rigorous clinical and translational perspective, contemporary therapeutic strategies must be strictly evaluated based on their evidence-graded clinical stages and mechanistic boundaries (Table II).

Table II. Clinical translational progress of mitochondrial-targeted and advanced metabolic therapies for MASLD/MASH.

A, Lifestyle intervention

Core target	Candidates	Mitochondrial and metabolic mechanisms	Highest clinical stage	Key clinical obstacles and limitations
Metabolic remodeling	Physical exercise	Stimulates hepatic mitochondrial biogenesis; restores systemic redox balance.	First-line recommendation	Low long-term patient compliance; limited capacity to directly reverse established advanced fibrosis.

B, Direct mitochondrial quality control

SIRT3-associated redox pathways	No selective clinical activator established	IDH2 deacetylation and SOD2-associated regulation support mitochondrial redox homeostasis and lipotoxic stress responses.	Preclinical mechanistic evidence	Requires liver-selective compounds and direct efficacy testing in MASH.
Antioxidant strategies	Vitamin E; silybin/phosphatidylcholine/vitamin E; MitoQ	Conventional antioxidant regimens have formulation-specific clinical data; mitochondria-targeted MitoQ reduced oxidative and inflammatory injury in a mouse NASH model.	Clinical studies for conventional regimens; MitoQ preclinical in NASH	Clinical antifibrotic efficacy is inconsistent, and evidence cannot be transferred across formulations.
Mild mitochondrial uncoupling	CRMP	Produces controlled proton leak and reduced hepatic lipid burden in rat and non-human-primate models.	Preclinical	Human efficacy and the therapeutic safety window remain unestablished.

C, Hepatocyte-autonomous protection

THR- β agonist	Resmetirom (MGL-3196)	Selectively targets hepatic THR- β , reduces liver fat and improves prespecified MASH histological endpoints.	FDA approved for an eligible noncirrhotic MASH population	Indication boundaries, adverse effects and long-term outcomes require continued monitoring.
ACC inhibitor	Firsocostat (GS-0976)	Inhibits ACC-dependent DNL and reduces hepatic fat.	Phase II evidence	Monotherapy can increase circulating triglycerides; combination benefit is regimen-specific.
Pan-PPAR agonist	Lanifibranor	Modulates PPAR- $\alpha/\gamma/\delta$ signaling and improves MASH activity and fibrosis-related histological endpoints.	Phase IIb efficacy; late-stage development	Weight gain, fluid retention and durability of histological benefit require monitoring.

D, Systemic metabolic retrograde driving

GLP-1-based therapy	Semaglutide-containing combination regimen	Primarily improves systemic energy balance and reduces substrate delivery to the liver; direct mitochondrial effects were not established.	Phase II evidence for the cited combination	The contribution of each drug and direct hepatocyte-autonomous effects remain uncertain.
Multi-incretin agonists	Tirzepatide/retatrutide	Dual or triple incretin-receptor agonism reduces body weight and hepatic metabolic burden; trial endpoints differ between agents.	Phase II (tirzepatide); phase IIa (retatrutide)	Long-term fibrosis and intrahepatic mitochondrial outcomes require follow-up.

Table II. Continued.

D, Systemic metabolic retrograde driving				
Core target	Candidates	Mitochondrial and metabolic mechanisms	Highest clinical stage	Key clinical obstacles and limitations
FGF21 analogues	Efruxifermin/ pegozafermin	Improve systemic metabolic measures, liver fat and histological endpoints in randomized studies.	Phase IIb efficacy; late-stage development	Chronic injection, durability, safety and cost remain practical limitations.

MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MitoQ, mitoquinone; mROS, mitochondrial reactive oxygen species; CRMP, controlled-release mitochondrial protonophore; FFA, free fatty acid; FDA, Food and Drug Administration; THR- β , thyroid hormone receptor- β ; ACC, acetyl-CoA carboxylase; DNL, *de novo* lipogenesis; GLP-1RA, glucagon-like peptide-1 receptor agonist; PPAR, peroxisome proliferator-activated receptor; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; FGF21, fibroblast growth factor 21.

Basic therapies and direct mitochondrial quality control (preclinical to early clinical)

Physical exercise: The cornerstone of endogenous mitochondrial adaptation. Regular physical exercise is a first-line intervention for MASLD and improves hepatic steatosis and insulin sensitivity. In experimental models, hepatocyte eNOS contributes to exercise-induced adaptations in hepatic mitochondrial function and autophagy, while broader evidence links exercise to enhanced hepatic fatty acid oxidation and reduced steatosis (73,74). The extent to which exercise alone reverses advanced fibrosis remains uncertain and adherence limits long-term effectiveness.

Evolution of antioxidants and mitochondrial-targeted redox strategies. Conventional vitamin E can improve biochemical and selected histological features in NASH, but treatment response and fibrosis benefit are variable (75). Silybin combined with phosphatidylcholine and vitamin E has also been evaluated in a randomized trial in NAFLD (76). Mitoquinone is designed to concentrate antioxidant activity within mitochondria and attenuated steatosis, necroinflammation and profibrogenic signaling in a mouse NASH model (77). These data support preclinical mitochondrial targeting but do not yet establish a consistent antifibrotic benefit in patients.

Modulating the mitochondrial proton motive force represents another strategy to reduce lipid burden and oxidative pressure. A controlled-release mitochondrial protonophore reversed diabetes and steatohepatitis in rats (78) and subsequently reduced dyslipidemia and hepatic steatosis in dysmetabolic non-human primates (79). These studies provide preclinical proof of concept; they should not be described as evidence of established clinical translation.

Sirtuin-related and natural-product metabolic remodeling. Reduced mitochondrial deacetylase activity and oxidative stress provide a rationale for targeting sirtuin-associated pathways, but direct clinical evidence for selective SIRT3 activators in MASH remains limited.

Among natural products, resveratrol has been studied across experimental and clinical liver-disease settings and may influence AMPK, sirtuin and antioxidant

pathways (80). The heterogeneity of formulations, doses and study models precludes assigning a single validated SIRT1/AMPK/Smad3/microRNA-141 mechanism to its effects in human MASH.

Hepatic focal metabolic targeting: Cell-autonomous mitochondrial protection (advanced clinical and approved stages). The core of this category lies in hepatocyte-directed metabolic regulation, in which pharmacological agents act on hepatic enzymes or nuclear receptors to reduce substrate overload and improve cellular bioenergetics.

Thyroid hormone receptor (THR)- β agonist: The milestone breakthrough of resmetirom. Resmetirom (MGL-3196) became the first FDA-approved pharmacotherapy for adults with noncirrhotic MASH and moderate-to-advanced fibrosis in 2024 (81). In the phase III MAESTRO-NASH trial, resmetirom increased the proportions of patients achieving MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of disease activity (82). A preceding 36-week phase II extension also demonstrated improvements in non-invasive efficacy measures (83). These data establish clinical efficacy within the studied population without implying universal reversal of advanced fibrosis.

Combined strategies involving acetyl-CoA carboxylase (ACC) inhibition. ACC inhibitors such as firsocostat reduce DNL and hepatic fat, but monotherapy can increase circulating triglycerides (84). A phase II trial subsequently evaluated combinations of semaglutide, cilofexor and firsocostat, supporting combination development while not establishing a specific synergy with THR- β agonists (85).

PPAR agonists restore metabolic transcription through multiple receptor isoforms. In the phase IIb NATIVE trial, the pan-PPAR agonist lanifibranor improved MASH activity and fibrosis-related histological endpoints (86). Additional analyses showed improvements in cardiometabolic measures (87). These findings support further late-stage development while avoiding claims that fibrosis reversal is already established for all patients.

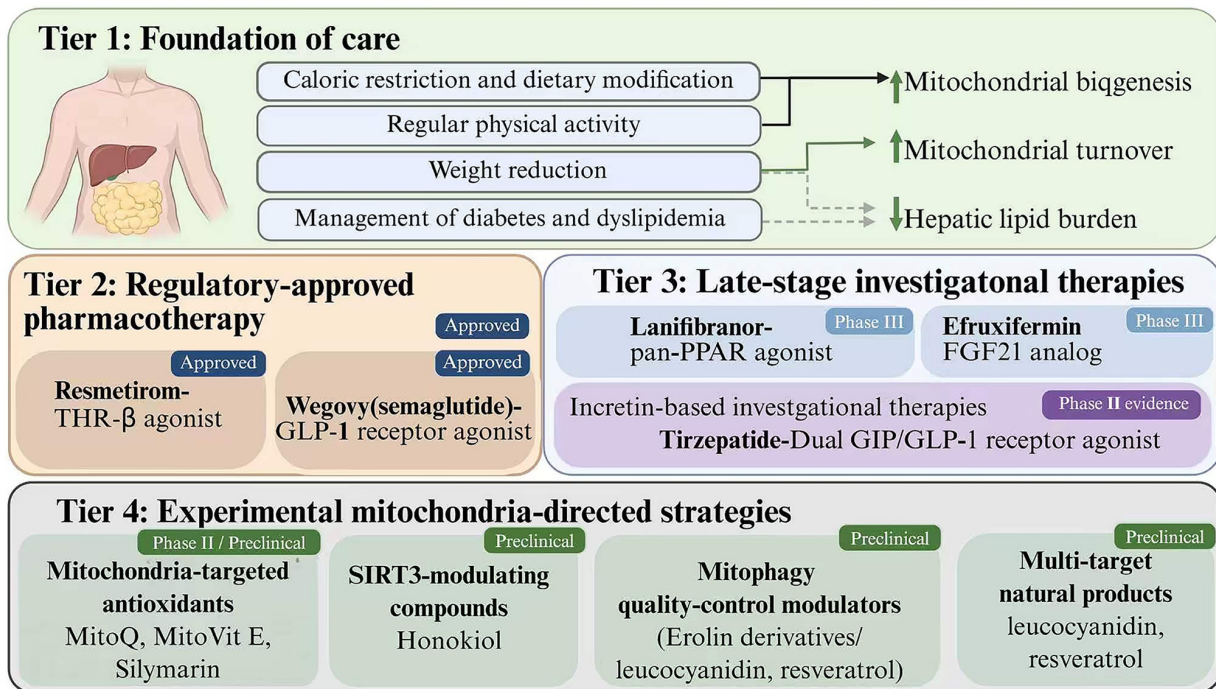


Figure 6. Evidence-graded therapeutic framework for MASLD/MASH. Tier 1 comprises lifestyle and cardiometabolic management, including physical activity and weight reduction (72,73). Tier 2 contains approved hepatocyte-directed therapy, represented here by resmetirom for eligible adults with noncirrhotic MASH and moderate-to-advanced fibrosis (80,81). Tier 3 comprises agents with randomized phase II/IIb evidence, including firsocostat-containing combinations, lanifibranor, tirzepatide, retatrutide, efruxifermin and pegozafermin (83-91). Tier 4 includes experimental mitochondria-directed approaches such as MitoQ and controlled-release mitochondrial protonophores, for which the cited MASH evidence remains preclinical (76-78). Conventional vitamin E or silybin-containing regimens and resveratrol have clinical or mixed translational evidence, but formulation-specific effects should not be generalized (74,75,79). MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; THR-β, thyroid hormone receptor-β; PPAR, peroxisome proliferator-activated receptor; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; FGF21, fibroblast growth factor 21; MitoQ, mitoquinone.

Systemic metabolic drivers: Predominantly non-cell-autonomous hepatic protection. Unlike hepatocyte-directed agents, these therapies primarily remodel metabolic flux in adipose tissue, muscle and the central nervous system, thereby reducing lipid delivery to the liver and indirectly relieving mitochondrial substrate pressure.

Lipid-clearing effects of glucagon-like peptide-1 receptor agonism and multi-incretin agonists. Recent phase II studies have demonstrated substantial improvements in hepatic metabolic and histological endpoints. Tirzepatide, a dual GIP/GLP-1 receptor agonist, achieved high rates of MASH resolution without worsening of fibrosis in patients with F2-F3 fibrosis (88), whereas the triple GIP/GLP-1/glucagon receptor agonist retatrutide produced marked reductions in liver fat in patients with MASLD (89).

These agents primarily reduce appetite, body weight, insulin resistance and systemic free-fatty-acid delivery to the liver. Although this metabolic unloading can protect hepatocytes from lipotoxic stress, the cited trials do not directly characterize autonomous effects on intrahepatic mitochondrial dynamics (90,91). Their hepatic benefit should therefore be described as predominantly systemic unless direct organelle-level evidence is available.

FGF21 analogs: Systemic metabolic improvement with histological efficacy. Pegozafermin and efruxifermin demonstrated promising histological efficacy in randomized phase IIb trials in NASH/MASH (90,91). These results support

continued late-stage development but do not by themselves establish phase III efficacy.

Earlier phase 1b/2a data for pegozafermin demonstrated reductions in liver fat and improvements in liver enzymes, lipids and adiponectin (92). These clinical pharmacodynamic findings do not directly prove activation of a hepatic PGC-1α/PPAR axis or brown-adipose thermogenesis; those mechanistic claims have therefore been removed (Fig. 6).

5. Discussion and concluding perspectives

The paradigm of MASLD pathogenesis has evolved from a linear model of lipid overload to a highly interconnected, non-linear network where mitochondrial dysfunction operates as the central rheostat. The structural and functional evolution of the intrahepatic mitochondrial network, progressing through a biphasic curve of early hormetic compensation to late bioenergetic failure, dictates the clinical transition from simple steatosis to MASH and progressive fibrosis.

Despite notable advances in characterizing downstream events such as mROS generation, lipid peroxidation (4-HNE/MDA formation) and organelle structural collapse (DRP1-mediated fission overactivation, UPR^{mt} decompensation and MAM-mediated Ca²⁺ overload), numerous key mechanistic gaps and translation barriers remain. First, the precise upstream triggers that dictate the transition from adaptive mitochondrial hypermetabolism to decompensated bioenergetic failure remain incomplete. Second, as highlighted

by the sirtuin epigenetic network, multi-compartmentalized enzymes such as SIRT4 and SIRT7 exhibit profound context-dependency and cell-type specificity, creating an urgent need for cell-specific and time-resolved genetic models to reconcile existing academic controversies.

Monotherapies rarely address all pathogenic facets of this complex metabolic disorder. The current pipeline includes hepatocyte-directed metabolic agents such as resmetirom and pan-PPAR agonists, as well as systemic metabolic drivers such as multi-incretins and FGF21 analogs. While systemic drivers reduce intrahepatic lipid partly through weight loss and improved peripheral metabolism, their direct long-term effects on hepatocyte organelle quality control require longitudinal study.

Consequently, the future of MASLD therapeutics lies in the rational design of personalized combination protocols. Pairing cell-autonomous mitochondrial stabilizers with systemic incretin therapies, tailored precisely to the body mass index, diabetic status and baseline fibrotic stage of a patient, will represent the true frontier of clinical precision medicine in overcoming this global metabolic epidemic.

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Availability of data and materials

Not applicable.

Authors' contributions

JC conceived and designed the study, performed the extensive literature review and drafted the primary manuscript as the principal author. HZ assisted in the literature screening, designed the thematic tables, prepared the figures and critically revised the manuscript for important intellectual content. HC revised the manuscript critically for important intellectual content and refined the mechanistic frameworks. WF and JL, serving as senior supervisors, provided overall strategic direction, critically reviewed the study design, critically revised the manuscript for important intellectual content and supervised the final refinement of the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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