



Review Article

The Role of Mitochondrial Complexes in Liver Diseases

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Abstract

Mitochondrial respiratory complexes (Complexes I–V) and their assembly into respiratory supercomplexes (SCs) are fundamental to liver bioenergetics, redox homeostasis, and metabolic adaptability. Disruption of these systems contributes to major liver diseases, including non-alcoholic fatty liver disease, alcoholic liver disease, drug-induced liver injury, viral hepatitis, and hepatocellular carcinoma, by impairing adenosine triphosphate synthesis, increasing oxidative stress, and altering metabolic pathways. Recent advances have clarified the structural-functional interdependence of individual complexes within SCs, revealing their dynamic remodeling in response to physiological stress and pathological injury. These insights open opportunities for clinical translation, such as targeting SC stability with pharmacological agents, nutritional strategies, or gene therapy, and employing mitochondrial transplantation in cases of severe mitochondrial failure. Precision medicine approaches, incorporating multi-omics profiling and patient-derived models, may enable individualized interventions and early detection using SC integrity as a biomarker. By linking molecular mechanisms to therapeutic strategies, this review underscores the potential of mitochondrial-targeted interventions to improve outcomes in patients with liver disease.

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Introduction

The liver, a vital organ responsible for metabolism and detoxification, is highly susceptible to damage from prolonged exposure to harmful substances such as alcohol, drugs, and toxins.¹ These agents induce oxidative stress by increasing intracellular reactive oxygen species (ROS) levels, which subsequently damage cell membranes, proteins, and DNA, ultimately leading to hepatocyte apoptosis or necrosis.² Mitochondrial dysfunction is a key factor in the onset and progression of liver injury. As the central hub of intracellular energy metabolism, mitochondria, when impaired, can cause reduced adenosine triphosphate (ATP) production,

exacerbated oxidative stress, and increased apoptosis. This disorder may be associated with mitochondrial DNA (mtDNA) mutations, protein synthesis defects, or decreased membrane potential.³ Emerging evidence shows that mitochondrial complexes often assemble into respiratory supercomplexes (SCs), which enhance electron transfer, reduce ROS generation, and stabilize individual complexes.⁴ Disruption of SCs has been increasingly recognized in liver diseases, highlighting the importance of mitochondrial structural integrity. An in-depth investigation of these mechanisms can provide insights into the pathogenesis of liver diseases and guide the development of novel therapeutic strategies.

Functions and biological significance of mitochondrial complexes

Mitochondrial complexes reside within the inner mitochondrial membrane and comprise five core complexes (I–V). These complexes function synergistically to transfer electrons from nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD) to oxygen, ultimately producing ATP to meet cellular energy demands. Each complex consists of specific subunits and carries out distinct redox reactions (Table 1).^{5–27}

Mitochondrial complex I

Mitochondrial complex I (NADH dehydrogenase) is the first enzyme complex in the mitochondrial electron transport chain (ETC) and the largest and most structurally intricate component of the chain. It facilitates electron transfer from NADH to coenzyme Q (CoQ) while concurrently pumping four protons into the mitochondrial intermembrane space, thereby establishing a proton gradient across the inner mitochondrial membrane. This gradient drives ATP synthase (complex V), a critical step in ATP production.^{28,29} In liver diseases, reduced complex I activity disrupts the NADH/NAD⁺ ratio, leading to redox imbalance, oxidative stress, and lipid peroxidation, which ultimately exacerbates hepatocyte injury.³⁰ Furthermore, complex I dysfunction undermines the integrity of the mitochondrial respiratory chain, reduces ATP synthesis, and aggravates metabolic dysregulation, intensifying liver damage.³¹ Complex I dysfunction is a key contributor to multiple liver diseases. In alcoholic liver disease and drug-induced liver injury (DILI), reduced complex I activity impairs mitochondrial electron transfer, increases ROS accumulation, and intensifies lipid peroxidation, leading to hepatocyte injury.^{32,33} In non-alcoholic fatty liver disease (NAFLD), complex I dysfunction is strongly linked to impaired fatty acid β -oxidation and mitochondrial dysfunction, serving as a critical driver of disease progression.^{34,35} In cirrhosis,

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Table 1. Overview of mitochondrial complexes I–V in liver diseases

Complex	Associated liver diseases	Clinical relevance / Therapeutic strategy
Complex I	ALD, ⁵ NAFLD, ⁶ cirrhosis, HCC ⁷	NAD ⁺ precursors, ⁸ CoQ10, ⁹ antioxidants, metformin
Complex II	HCC, ¹⁰ metabolic liver disease ¹¹	SDHIs (inhibitors or modulators), ¹² metabolic control of succinate ¹³
Complex III	NAFLD, ¹⁴ IRI, ¹⁵ DILI ¹⁶	CoQ10 supplementation, NAD ⁺ boosting, ¹⁷ ROS scavengers ¹⁸
Complex IV	Fibrosis, ¹⁹ viral hepatitis, ²⁰ IRI ²¹	Oxygen delivery modulation, ²² copper cofactors, ²³ NO donors ²⁴
Complex V	Hepatitis, ²⁵ ALD ²⁶	Creatine, pyruvate supplementation, mitoprotective peptides ²⁷

ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NAD, nicotinamide adenine dinucleotide; CoQ, coenzyme Q; SDHIs, succinate dehydrogenase inhibitors; IRI, ischemia-reperfusion injury; DILI, drug induced-liver injury; ROS, reactive oxygen species; NO, nitric oxide.

reduced complex I activity worsens oxidative stress, further compromising hepatocyte function and accelerating disease progression.³⁶ In hepatocellular carcinoma, complex I dysfunction may induce redox imbalance, promoting tumor cell proliferation and metastasis.³⁷ Viral infections may also directly or indirectly affect complex I function. For example, hepatitis C virus infection has been shown to cause abnormal mitochondrial function, including decreased complex I activity and increased ROS production.³⁸ These findings highlight the essential role of mitochondrial complex I in the initiation and progression of liver diseases.

Mitochondrial complex II

Mitochondrial complex II (succinate dehydrogenase, SDH) is a nuclear-encoded enzyme that bridges the tricarboxylic acid (TCA) cycle and the ETC.³⁹ Unlike other ETC complexes, complex II does not translocate protons across the mitochondrial membrane. Instead, it catalyzes the oxidation of succinate to fumarate, reducing FAD to FADH₂ and transferring electrons to CoQ.⁴⁰ This provides an alternative pathway for electrons to bypass complex I and enter the ETC, ensuring continuity of energy metabolism.⁴¹ As a critical link between the TCA cycle and the ETC, complex II plays a key role in maintaining mitochondrial metabolic stability and cellular bioenergetic balance, particularly when NADH oxidation is impaired or its supply is insufficient. By mediating succinate metabolism, complex II integrates the TCA cycle, fatty acid oxidation, and the ETC, ensuring efficient utilization of carbon substrates and sustaining ATP synthesis.⁴² However, long-term or excessive use of SDH inhibitors may lead to abnormal accumulation of succinate, disrupting mitochondrial oxidative metabolism. This effect is especially pronounced in metabolically susceptible individuals and may result in severe adverse consequences.⁴⁰ Notably, while insufficient SDH activity can impair mitochondrial function, excessive SDH activity may also induce metabolic imbalances. Therefore, appropriate regulation of complex II activity may represent a potential strategy for treating metabolic disorders.⁴³ Dysfunction of complex II is linked not only to hereditary mitochondrial diseases but also to the pathogenesis of cancer, neurodegenerative disorders, and metabolic syndromes. Research indicates that SDH functions as a tumor suppressor, whereas its metabolite, succinate, may act as an oncometabolite promoting tumor progression under specific circumstances.^{44,45} In HCC tumor specimens, succinate dehydrogenase subunit B (SDHB) expression is reduced by 40%.⁴⁶ Reduced SDHB expression disrupts mitochondrial ETC function, leading to the Warburg effect. This metabolic reprogramming promotes oncogenic processes and strengthens the malignant phenotype of HCC cells.⁴⁷ Such a metabolic shift may represent an adaptive strategy employed by tumor cells to evade immune detection and enhance resistance to apoptosis.⁴⁸

Mitochondrial complex III

Mitochondrial complex III (cytochrome bc₁ complex) is a crucial component of the ETC, responsible for transferring electrons from CoQ to cytochrome c while actively pumping protons into the intermembrane space. This process generates the proton gradient essential for ATP synthesis.^{49,50} When complex III activity decreases, electron transfer efficiency declines, leading to a significant increase in oxidative stress and worsening mitochondrial damage.⁵¹ Given that the liver is one of the most metabolically active organs, its mitochondria are highly sensitive to oxidative stress. Impaired complex III function results in excessive mitochondrial ROS generation, which damages cellular membranes, proteins, and DNA, ultimately causing hepatocyte injury and inflammation.⁵² Additionally, complex III dysfunction is closely associated with energy metabolism disorders in liver diseases. Patients often exhibit mitochondrial dysfunction, leading to reduced ATP synthesis, and a further decline in complex III activity exacerbates energy insufficiency, disrupting normal hepatocyte physiological functions.⁵³ Strategies to enhance mitochondrial function, such as supplementation with NAD⁺ precursors (e.g., nicotinamide riboside) or CoQ, can help maintain complex III activity and improve liver metabolic function.⁵⁴ Notably, complex III dysfunction not only affects energy metabolism but also worsens liver injury by promoting apoptosis. Reduced complex III activity increases electron leakage, resulting in cytochrome c release, activation of caspase cascades, and ultimately triggering apoptosis. In liver diseases, apoptosis is a key driver of hepatocyte injury, fibrosis, and disease progression.⁵⁵ Furthermore, complex III dysfunction may contribute to the development and progression of liver tumors. Studies indicate that decreased complex III activity is closely related to tumor cell proliferation, invasion, and metastasis, potentially promoting liver cancer development by regulating metabolic reprogramming, redox balance, and signal transduction pathways.⁵⁶

Mitochondrial complex IV

Mitochondrial complex IV (cytochrome c oxidase, COX) serves as the final enzyme in the ETC, facilitating electron transfer to oxygen to form water. Simultaneously, it pumps protons into the intermembrane space, sustaining the proton gradient required for ATP synthesis.⁵⁷ COX consists of multiple subunits, among which the catalytic subunit containing copper ions plays a crucial role in electron transfer.⁵⁸ COX activity is pivotal in regulating mitochondrial oxidative phosphorylation (OXPHOS) and cellular energy homeostasis, and its dysfunction is implicated in multiple liver pathologies. A decrease in COX activity can impair OXPHOS in hepatocytes, reduce ATP synthesis, disrupt intracellular energy metabolism, and exacerbate liver injury.^{59,60} During liver fibrosis, reduced COX activity may lead to abnormal extracellular matrix deposition, accelerating pathological progression.⁶¹ Elevated

oxidative stress is closely associated with COX dysfunction. Excessive ROS accumulation not only damages hepatocytes but may further disrupt mitochondrial membrane potential, leading to mitochondrial dysfunction.⁶² In liver cancer, abnormal COX activity may enable cancer cells to adapt to hypoxic environments, alter metabolic pathways, and consequently influence tumor growth, invasion, and metastasis.⁶³ In hepatic ischemia-reperfusion injury (IRI), decreased COX activity exacerbates mitochondrial damage, rendering hepatocytes more susceptible to apoptosis or necrosis and worsening tissue injury.⁶⁴ In drug-induced DILI, doxorubicin can significantly inhibit complex IV activity, disrupting cytochrome c redox balance, promoting activation of apoptosis-related markers such as caspase 3, and ultimately triggering cellular energy metabolism disorders and apoptosis.⁶⁵

Mitochondrial complex V

Mitochondrial complex V, or ATP synthase, represents the final enzyme of the OXPHOS system. It harnesses the proton gradient generated by the ETC to drive ATP synthesis from adenosine diphosphate and inorganic phosphate, fulfilling cellular energy demands.⁶⁶ In numerous liver diseases, a decline in complex V activity disrupts ATP synthesis, compromising cellular energy supply and exacerbating hepatocyte dysfunction. In patients with chronic hepatitis or liver cirrhosis, reduced ATP production weakens hepatocyte resilience, making cells more susceptible to pathological damage.^{61,67} Moreover, decreased ATP levels reduce the cell's antioxidant capacity, impairing free radical scavenging and exacerbating oxidative stress, further impairing mitochondrial function and aggravating liver damage.⁶⁸ Complex V dysfunction also closely relates to apoptosis. Reduced complex V activity can alter mitochondrial membrane potential, activating apoptotic signaling pathways, such as the caspase cascade, ultimately inducing programmed cell death in hepatocytes.⁶⁹ This mechanism is particularly prominent in liver cancer and cirrhosis, suggesting that abnormal complex V activity contributes significantly to disease onset and progression. Additionally, complex V dysfunction may interfere with autophagy, an essential mechanism for maintaining cellular homeostasis. Autophagy plays a crucial role in clearing damaged mitochondria and regulating energy balance. When complex V activity is impaired, autophagic flux may be inhibited, leading to the accumulation of damaged organelles and further exacerbating hepatocyte dysfunction.⁷⁰

Structural and functional interdependence of mitochondrial complexes

Mitochondrial OXPHOS has traditionally been understood as a linear sequence of electron transfers through five separate complexes (I–V) embedded in the inner mitochondrial membrane. However, emerging structural and biochemical evidence has revised this view, showing that ETC complexes do not function as isolated units but rather as organized respiratory SCs, often referred to as “respirasomes”.⁷¹ These supramolecular assemblies, mainly consisting of complex I, complex III, and complex IV, facilitate more efficient electron transport, limit ROS production, and stabilize individual complex subunits.⁷²

Structure and composition of respiratory SCs

Respiratory SCs are dynamic assemblies primarily composed of complex I, complex III dimer (III₂), and complex IV in various stoichiometries. The most common mammalian respirasome identified through cryo-electron microscopy is the com-

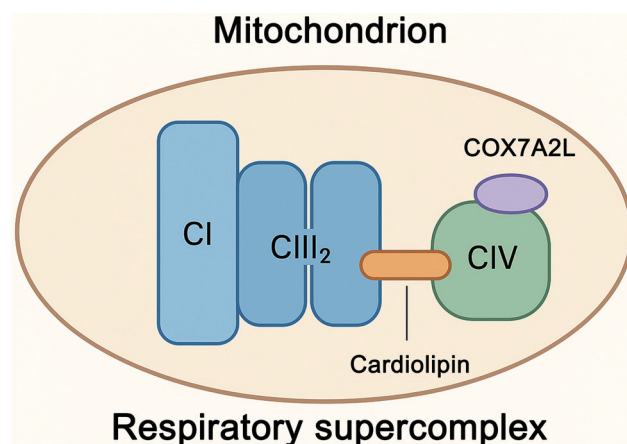


Fig. 1. The structure of mitochondrial supercomplexes. CI, complex I; CIII₂, complex III dimer; CIV, complex IV.

plex I–III₂–IV.⁷³ These assemblies are stabilized by specific lipids, especially cardiolipin, and accessory proteins such as COX7A2L (SCAF1), which anchor complex IV to complex III₂ and modulate SC stability (Fig. 1).⁷⁴ The formation of SCs optimizes spatial proximity among ETC components, facilitating direct substrate channeling between complexes, minimizing electron leakage, and preventing excess ROS formation, particularly important in metabolically active organs such as the liver. In liver diseases, including IRI and NAFLD, disruption of SC assembly has been reported, further implicating mitochondrial architecture in disease pathogenesis and highlighting potential targets for therapeutic stabilization.^{75,76}

Significance and dependency of respiratory SCs in liver disease

In the liver, the exceptionally high metabolic demand requires efficient electron transport and ATP synthesis. Respiratory SCs enhance mitochondrial efficiency by facilitating electron flux, optimizing proton pumping, and minimizing ROS leakage. Evidence from mouse hepatocyte studies demonstrates that SC destabilization is closely associated with mitochondrial dysfunction, ATP depletion, and elevated ROS production, processes central to the pathogenesis of hepatic disorders.^{77,78} In pathological conditions such as NASH and DILI, oxidative damage or depletion of cardiolipin can compromise SC integrity, leading to the disassembly of complex I and a subsequent rise in oxidative stress.^{79,80} These structural disruptions are further associated with metabolic inflexibility and impaired adaptive responses to nutrient overload or oxidative insults, hallmark features of metabolic liver diseases.

The stability and functional integrity of individual ETC complexes are highly dependent on their incorporation into SCs. Complex I, for example, is inherently unstable in isolation, with degradation markedly accelerated when not embedded within an SC. Conversely, SC assembly promotes the biogenesis and stabilization of complexes III and IV, highlighting a mutual structural dependency that may function as a mitochondrial quality control mechanism.^{81,82} This intricate interdependence means that dysfunction in one complex, such as mutations in complex III, can trigger secondary destabilization of complex I or IV, creating a cascade of mitochondrial defects. Such interconnected failure mechanisms may account for the non-linear and disproportionate phenotypic manifestations observed in certain mitochondrial pathologies and liver diseases.

Table 2. The liver model, complex effects, and intervention strategies applied in research

Liver disease model	Cell/Animal type	Targeted complex
NAFLD ¹⁰⁴	HFD-fed mice; AML12 cells	I, III, IV
DILI ^{38,105}	APAP-treated mice; HepG2 cells	I, III
IRI ¹⁰⁶	Ischemia-reperfusion rat model	III, IV
HCC ¹⁰⁷	HepG2, mouse xenografts	II, V
Cholestatic liver disease ^{108,109}	Bile duct ligation mice; HepaRG cells	I, III, V
Cirrhosis ^{110,111}	CCl ₄ model in rats	I, V

NAFLD, non-alcoholic fatty liver disease; HFD, high-fat diet; I-V, complex I-V; DILI, drug induced-liver injury; APAP, acetaminophen; IRI, ischemia-reperfusion injury; HCC, hepatocellular carcinoma; CCl₄, carbon tetrachloride.

Supercomplex dynamics, disruption, and therapeutic potential

The architecture of respiratory SCs is highly dynamic, undergoing modulation in response to physiological conditions such as nutritional state, oxygen availability, and metabolic stress.⁸³ In the early stages of liver disease, including simple steatosis, hepatocytes may reorganize SCs as a compensatory adaptation to maintain ATP production. However, persistent insults, such as chronic injury or lipid overload, progressively disrupt SC structure, leading to impaired respiratory efficiency and mitochondrial dysfunction.^{84,85} For instance, in fatty liver, prolonged ethanol exposure impairs cardiolipin remodeling enzymes such as Tafazzin, resulting in SC disintegration and mitochondrial fragmentation.^{86,87} Similarly, in NASH models, high-fat diets hinder SC assembly, exacerbating hepatic inflammation and fibrosis.⁸⁸

Understanding the structural-functional coupling within SCs opens new avenues for therapeutic intervention, as stabilizing these assemblies offers a strategy to restore mitochondrial function without directly modifying individual complex activities. Potential approaches include: cardiolipin-stabilizing agents such as the SS-31 peptide, which maintain SC cohesion and reduce ROS production;⁸⁹ nutritional interventions, including ketogenic diets and omega-3 fatty acids, which enhance SC assembly;^{90,91} and gene therapies aimed at restoring essential SC assembly factors such as SCAF1 in genetically susceptible individuals.⁹² Furthermore, SC integrity holds potential as a biomarker for mitochondrial health, enabling early detection of mitochondrial dysfunction in chronic liver diseases. Cutting-edge imaging and proteomics technologies now permit accurate quantification of SC abundance and configuration in liver biopsies and patient-derived organoids, bridging mechanistic insights and clinical translation.^{93,94}

Mitochondrial complex alterations in liver injury

The pathophysiological progression of hepatic injury is closely linked to dynamic alterations in mitochondrial complex functionality. During early injury phases, transient enhancement of mitochondrial complex activity serves as a compensatory response to heightened metabolic demands. However, this adaptive mechanism progressively deteriorates with disease advancement, ultimately leading to bioenergetic failure through impaired ATP synthesis and disrupted cellular energy regulation.^{95,96}

The cascade of mitochondrial complex dysfunction during hepatic injury unfolds through multiple mechanisms. Primarily, depolarization of the mitochondrial membrane potential emerges as an early sentinel event, disrupting electrochemical gradients and directly compromising ETC efficiency and

OXPHOS capacity.⁹⁷ Concurrently, marked attenuation of respiratory chain activity, particularly in complexes I and III, is linked to oxidative post-translational modifications of protein subunits, impaired cofactor biogenesis, and progressive mtDNA mutation accumulation.^{56,98} As injury progresses, the resulting oxidative stress within the mitochondrial matrix exerts a triple pathogenic impact: excessive ROS generation overwhelms endogenous antioxidant defenses, induces phospholipid membrane peroxidation and protein carbonylation, and directly destabilizes mitochondrial genomic integrity.³⁵ At irreversible stages, maladaptive rewiring of mitochondrial quality control manifests through hyperactivated mitophagic flux and dysregulated apoptotic signaling, collectively driving cristae collapse and depletion of bioenergetic reserves.^{99,100} Ultimately, exponential escalation of mtDNA mutational burden establishes a self-reinforcing pathological cycle, in which disrupted respiratory SC assembly and defective synthesis of 13 ETC-essential polypeptides collectively dismantle the mitochondrial bioenergetic network.^{101–103} These interlocking mechanisms, from molecular perturbations to organelle-level failure, orchestrate a systematic progression toward mitochondrial functional collapse, exemplifying the hierarchical integration of redox imbalance and systemic energetic catastrophe.

Collectively, hepatic injury is fundamentally characterized by progressive deterioration of mitochondrial complex structure and function. These multidimensional alterations exhibit dual significance: first, the extent of mitochondrial damage directly correlates with disease severity; second, it exacerbates maladaptive progression by compromising energy transduction efficiency in the OXPHOS system and amplifying stress signaling cascades, such as mitochondrial-derived ROS. Crucially, mitochondrial complex dysfunction not only serves as an early diagnostic biomarker but also acts as a pathogenic catalyst by disrupting respiratory SC assembly and promoting mtDNA mutation accumulation, establishing a self-perpetuating “damage–dysfunction–reinforced damage” positive feedback loop that mechanistically links bioenergetic failure to hepatic deterioration.

From mechanisms to therapy: Targeting mitochondrial complexes in liver disease

Mitochondrial dysfunction has emerged as a central mechanism underlying various forms of liver injury, including NAFLD, DILI, IRI, HCC, and cirrhosis (Table 2).^{38,104–111} Among mitochondrial components, complexes I–V serve not only as key bioenergetic modules but also as regulators of redox signaling, apoptosis, and cellular adaptation. Therefore, therapeutic targeting of mitochondrial complexes represents a promising avenue for disease modification. In recent years, strategies ranging from pharmacological modulation and

metabolic supplementation to organelle transplantation and gene therapy have been explored. Translating these interventions from mechanistic insight to clinical practice requires careful evaluation of their feasibility, delivery methods, and compatibility with individualized medicine.

Mitochondrial transfer therapy: A novel frontier

Mitochondrial transfer therapy, defined as the exogenous transplantation of functional mitochondria into damaged cells, has emerged as a compelling therapeutic strategy to restore bioenergetic function and cellular viability.^{112–114} In the liver, where energy metabolism is tightly coupled with detoxification, protein synthesis, and immune regulation, mitochondrial transfer may provide rapid bioenergetic rescue in acute injury settings such as IRI, acetaminophen overdose, or fulminant hepatic failure.

Several experimental models have demonstrated the efficacy of mitochondrial transfer in reversing hepatic mitochondrial dysfunction. For instance, injection of intact mitochondria isolated from healthy hepatocytes into damaged liver tissues restored ATP production, reduced oxidative stress, and prevented hepatocyte death.^{115,116} In a mouse model of acetaminophen-induced liver injury, mitochondrial transplantation significantly improved survival and reduced serum alanine aminotransferase/aspartate aminotransferase levels, demonstrating hepatoprotective effects.¹¹⁷ Mechanistically, the internalized mitochondria were shown to integrate with host mitochondrial networks, restore membrane potential, and reinitiate mitochondrial biogenesis via PGC-1 α and TFAM activation.^{118–120}

Despite promising preclinical outcomes, several translational challenges remain. Firstly, the delivery route must ensure mitochondrial viability and tissue-specific targeting. While intravenous administration has shown effectiveness in animal models, its safety and efficacy in humans require clinical validation.^{121–124} Secondly, donor mitochondrial source, immunogenicity, and quality control must be standardized to minimize rejection or off-target effects.^{125,126} Thirdly, optimal dosing regimens and timing post-injury are yet to be defined.¹²⁷ Currently, early-phase clinical trials evaluating autologous mitochondrial transfer in cardiac and renal ischemia are ongoing, potentially laying the groundwork for future hepatology applications.^{128,129}

Pharmacological and precision medicine for mitochondrial dysfunction

Modulating the activity of ETC complexes through pharmacological agents or nutritional supplements is an active area of investigation, with growing evidence supporting their role in mitigating mitochondrial dysfunction in liver diseases.^{59,130} NAD⁺ precursors, such as nicotinamide riboside and nicotinamide mononucleotide, have shown potential in restoring complex I function and enhancing OXPHOS, particularly in NAFLD and aging-related hepatic disorders. Ongoing clinical trials (NCT04571008) are evaluating their effects on liver fat content and mitochondrial health in humans.¹³¹ Coenzyme Q10, an essential electron carrier between complexes I/II and III, has been clinically assessed for its hepatoprotective properties, demonstrating improvements in liver function markers and oxidative stress parameters in NAFLD patients. However, optimal dosing regimens and long-term safety remain under investigation.¹³² Other promising modulators include resveratrol, which activates the SIRT1/PGC-1 α axis to promote mitochondrial biogenesis and alleviate hepatic steatosis, and creatine, which stabilizes ATP buffering and supports complex V function.^{133,134}

Despite these advances, clinical efficacy is often limited by poor bioavailability, insufficient tissue specificity, and inter-individual variability.^{135–137} Overcoming these barriers will require the development of advanced drug delivery systems, including liver-targeted nanoparticles for mitochondrial delivery, mitochondria-penetrating peptides capable of traversing the inner membrane, and prodrugs selectively activated within the oxidative environment of damaged hepatocytes.

Given the heterogeneity of liver diseases, precision medicine approaches are critical for effective and individualized interventions.¹³⁸ Mitochondrial complex defects in NAFLD may differ fundamentally from those in HCC or cholestatic liver diseases, necessitating targeted therapeutic strategies.¹³⁹ Integrating multi-omics profiling, including transcriptomics, metabolomics, and proteomics, enables identification of complex-specific dysfunction signatures and stratification of patient subgroups most likely to benefit from targeted therapy. In parallel, genomic sequencing and bioinformatics tools can uncover mutations or polymorphisms in ETC subunits, such as SDHB in HCC or ATP5B in metabolic liver disease, which may serve as biomarkers for therapeutic selection and prognosis prediction. Patient-derived organoids and induced pluripotent stem cell-based liver models offer translational platforms for preclinical testing of mitochondrial-targeted interventions in a personalized manner. Ultimately, clinical feasibility will depend on practical considerations, including the ability to titrate dosing based on mitochondrial function, ensuring long-term safety, particularly regarding off-target ROS generation, developing combination regimens that address both mitochondrial dysfunction and inflammation, and achieving cost-effectiveness and scalability, especially in resource-limited settings.

Emerging insights into mitochondrial complexes in liver disease

Recent advances in mitochondrial biology have significantly enhanced our understanding of mitochondrial complex dysregulation in hepatic pathophysiology. Accumulating evidence demonstrates that dynamic alterations in mitochondrial complex activity strongly correlate with histological grading of liver injury. Suppression of mitochondrial complex function during hepatic damage directly compromises ATP biosynthesis, establishing a causal relationship between bioenergetic failure and disrupted cellular metabolism. Notably, in NAFLD, impairment of mitochondrial complexes induces redox imbalance through defective electron transport, creating a self-perpetuating cycle of oxidative damage and hepatocyte degeneration.¹⁴⁰

Critical pathophysiological insights emerge from investigations into mitochondrial enzyme stoichiometry. Quantitative proteomic analyses reveal marked dysregulation of core respiratory components, particularly complexes I and IV, across various liver pathologies. In HCC, downregulation of complex I and IV subunits correlate with diminished ETC efficiency, creating a metabolic environment that promotes tumor proliferation and metastatic progression.^{141,142}

The redox environment of the mitochondrial ETC has emerged as a key determinant of disease pathogenesis. Hepatic disorders are consistently associated with disruption of redox homeostasis within cristae compartments, significantly affecting ETC function. During fibrotic remodeling, disruption of redox balance across mitochondrial complexes drives excessive superoxide leakage, triggering ROS-mediated amplification of parenchymal injury via lipid peroxidation cascades.¹⁴³

Of particular therapeutic relevance are the regulatory

networks governing mitochondrial complex dynamics. Multiple evolutionarily conserved pathways, including PI3K/Akt, mTOR, and AMPK, have been identified as master regulators of respiratory complex biogenesis and turnover. In HCC models, constitutive activation of PI3K/Akt signaling induces proteasomal degradation of complex I subunits through phosphorylation-dependent ubiquitination, thereby reprogramming cellular metabolism to support neoplastic growth and invasion.^{144–146}

Therapeutic prospects of targeting mitochondrial complexes

Targeting mitochondrial complexes has emerged as a promising therapeutic strategy for liver diseases. As central components of the ETC, mitochondrial complexes demonstrate functional impairments that are mechanistically associated with hepatic pathogenesis. Interventions directed at these complexes can correct metabolic abnormalities at their biochemical source, thereby restoring hepatic functionality. For instance, CRISPR/Cas9-mediated gene editing enables precise repair of pathogenic mtDNA mutations, effectively reversing complex dysfunction and alleviating disease symptoms.^{147,148}

Recent progress in molecular biology has accelerated the development of mitochondrial complex-targeted therapies. Specific antioxidants targeting complex I components (NADH dehydrogenase and CoQ) effectively neutralize ROS in hepatocytes, attenuating oxidative damage.^{149–153} Pharmacological agents such as rofecoxib enhance complex I activity, demonstrating therapeutic potential for metabolic liver disorders.^{154,155} Inhibitors of complex III reduce cellular redox potential, suppressing tumor progression,¹⁵⁶ while moderate complex III inhibition decreases oxidative stress in hepatic injury models.^{157,158} Similarly, complex IV-targeted antioxidants mitigate oxidative hepatocyte damage, promoting functional recovery.¹⁵⁹

This therapeutic approach demonstrates significant clinical promise through its multifaceted advantages. The foremost strength lies in exceptional molecular specificity achieved via direct targeting of mitochondrial complexes, effectively circumventing off-target effects on healthy cellular components. Complementing this precision, the inherent functional diversity among different complexes enables tailored therapeutic strategies aligned with individual pathophysiological profiles. Furthermore, comparative pharmacological analyses reveal superior safety margins over conventional treatments, particularly in minimizing systemic toxicity. However, translational implementation faces several critical challenges. Chief among these is interindividual heterogeneity in complex expression patterns, necessitating sophisticated pharmacogenomic approaches for dose optimization.^{160–162} Additionally, formulation challenges persist due to suboptimal pharmacokinetic properties, including reduced bioavailability and chemical instability. Of particular concern is emerging evidence of adaptive metabolic reprogramming in chronic disease states, which may undermine long-term therapeutic efficacy. Despite these challenges, targeted modulation of mitochondrial complexes remains a promising area of hepatology research, with the potential to redefine current treatment paradigms by integrating mechanistic precision and metabolic restoration.

Mitochondrial complexes are crucial for sustaining hepatocyte energy metabolism, oxidative balance, and overall cellular viability. Dysfunction of these complexes disrupts ATP synthesis, triggers apoptosis and autophagy dysregulation, and accelerates liver disease progression. Therefore, investi-

gating the mechanisms of mitochondrial complex dysfunction and their relationship with liver diseases will deepen our understanding of liver pathology and facilitate the development of targeted therapeutic approaches.

Conclusions

Emerging evidence underscores mitochondrial complexes and respiratory SCs as central regulators of hepatic bioenergetics, redox balance, and metabolic adaptability. Their structural-functional interdependence ensures efficient electron transport and ATP synthesis while maintaining resilience against oxidative and metabolic stress. Disruption of complex integrity, as observed in NAFLD, alcoholic liver disease, and other liver pathologies, compromises energy metabolism and amplifies oxidative damage, thereby accelerating disease progression. Therapeutically, strategies that stabilize SC architecture, enhance specific complex activity, or restore essential assembly factors hold promise for mitigating mitochondrial dysfunction. Integrating these approaches within precision medicine frameworks could enable targeted, patient-specific interventions, offering a pathway toward improved outcomes in diverse liver diseases.

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Conflict of interest

The author has no conflicts of interest related to this publication.

Author contributions

HA is the sole author of the manuscript and approved the final version of the manuscript.

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