Mitochondrial quality control in acute liver injury and its therapeutic implications (Review)

ZIQIANG CHEN[1], YUNHE WANG[2], YIJING LI[3], GANG CONG[4], YUNHANG CHU[1], YUNHUI BAI[1], YISHUO ZHANG[5] and LIYA ZHOU[3]

[1]College of Traditional Chinese Medicine, Changchun University of Chinese Medicine, Changchun, Jilin 130117, P.R. China; [2]Department of Endocrinology, Metabolism and Gastroenterology, The Third Affiliated Clinical Hospital of Changchun University of Chinese Medicine, Changchun, Jilin 130022, P.R. China; [3]College of Basic Medical Sciences, Changchun University of Chinese Medicine, Changchun, Jilin 130117, P.R. China; [4]Department of Digestive Endoscopy, Songyuan Jilin Oilfield Hospital, Songyuan, Jilin 138099, P.R. China; [5]College of Pharmacy, Changchun University of Chinese Medicine, Changchun, Jilin 130117, P.R. China

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Abstract. Acute liver injury (ALI) is a clinically important syndrome with limited mechanism-based therapies. Notably, mitochondrial dysfunction is increasingly recognized as a central driver of hepatocellular damage and repair failure. The present narrative review aims to summarize the current evidence on mitochondrial quality control (MQC) in ALI, with an emphasis on mitophagy, mitochondrial biogenesis, mitochondrial dynamics, etiology-specific regulation and therapeutic implications. For the present review, relevant experimental and translational studies addressing MQC-related mechanisms and interventions in major forms of ALI, including drug-induced liver injury, ischemia-reperfusion injury and viral ALI, were reviewed and integrated. The findings indicated that MQC operates as an interconnected network rather than as isolated pathways. Mitophagy, mitochondrial dynamics and mitochondrial biogenesis are temporally coordinated to remove damaged mitochondria, remodel mitochondrial networks and restore bioenergetic capacity. However, MQC responses differ across ALI etiologies, and inappropriate or excessive activation may become maladaptive. In conclusion, understanding MQC as a dynamic and context-dependent repair system may provide a conceptual basis for precision interventions in ALI. Future studies should clarify spatiotemporal MQC regulation, establish reliable biomarkers and validate MQC-targeted therapies in clinically relevant settings.

Correspondence to: Dr Yishuo Zhang, College of Pharmacy, Changchun University of Chinese Medicine, 1035 Boshuo Road, Jingyue National High-Tech Industrial Development Zone, Changchun, Jilin 130117, P.R. China
E-mail: 202400904@ccucm.edu.cn

Professor Liya Zhou, College of Basic Medical Sciences, Changchun University of Chinese Medicine, 1035 Boshuo Road, Jingyue National High-Tech Industrial Development Zone, Changchun, Jilin 130117, P.R. China
E-mail: zhouliya0919@163.com

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Contents

1. Introduction

Acute liver injury (ALI) is a common and potentially life-threatening clinical syndrome characterized by rapid hepatocellular damage and abrupt deterioration of liver function. It can have diverse etiologies, including drug-induced toxicity, ischemia-reperfusion injury (IRI), viral infection, alcohol exposure and immune-mediated insults (1). In severe cases, ALI can progress to acute liver failure, which is associated with high morbidity and mortality rates. Supportive interventions, such as withdrawal of offending agents, hepatoprotective therapies, artificial liver support systems and liver transplantation, have improved clinical outcomes to some extent; however, effective mechanism-based therapies that directly promote hepatocellular recovery remain limited (2,3). Therefore, elucidating the cellular and molecular mechanisms underlying liver injury and repair is crucial.

Mitochondria serve a key role in hepatocyte physiology by regulating energy metabolism, redox balance and responses to cellular stress (4). Notably, mitochondrial dysfunction is a major driver of hepatocyte injury and death in ALI (5). Loss of mitochondrial membrane potential, excessive production of reactive oxygen species (ROS), impaired oxidative phosphorylation and mitochondrial DNA damage collectively contribute

to metabolic failure and the amplification of cellular injury (6). The degree of mitochondrial dysfunction is closely associated with disease severity and recovery outcomes in experimental models of ALI, whereas preservation or restoration of mitochondrial function can attenuate liver injury and promote hepatic recovery, underscoring the pivotal role of mitochondrial homeostasis in hepatocyte survival and repair (7,8).

Mitochondrial quality control (MQC) is an integrated regulatory system that preserves mitochondrial integrity and function through three interconnected processes: Mitophagy, mitochondrial biogenesis and mitochondrial dynamics. Mitophagy selectively removes damaged mitochondria to limit cellular stress, whereas mitochondrial biogenesis replenishes mitochondrial content and restores bioenergetic capacity, and mitochondrial dynamics remodel the mitochondrial network through coordinated fission and fusion (9). Together, these processes maintain mitochondrial homeostasis under physiological and pathological conditions (10).

Accumulating evidence has indicated that MQC dysregulation contributes to the initiation and progression of ALI, whereas appropriately regulated MQC responses facilitate mitochondrial turnover, network remodeling and hepatocellular recovery (11,12). Notably, MQC activation is not uniform across different forms of ALI. Variations in the etiology, severity and temporal stage of the injury influence the engagement of mitophagy, mitochondrial biogenesis and mitochondrial dynamics. Specifically, mild or early-stage injury may induce adaptive mitophagy, compensatory mitochondrial biogenesis and balanced mitochondrial fission-fusion remodeling, whereas severe or prolonged injury may lead to impaired mitophagic clearance, insufficient mitochondrial biogenesis and excessive mitochondrial fragmentation. These context-dependent differences may partly explain the heterogeneous disease outcomes of ALI (13). Rather than representing isolated protective mechanisms, MQC is increasingly recognized as a dynamic and context-dependent regulatory network in which individual components are temporally and functionally integrated to adapt mitochondrial homeostasis to distinct cellular stresses (14,15).

The novelty of the present narrative review lies in the integration of MQC as a temporally organized and etiology-dependent repair system in ALI, rather than as a set of isolated mitochondrial pathways. Compared with previous reviews (7,8) that have primarily focused on mitochondrial dysfunction or individual MQC components in liver diseases, the current review emphasizes the coordinated 'clearance-remodeling-regeneration' sequence, compares MQC patterns across different ALI etiologies and discusses the translational barriers that limit MQC-targeted therapies. Here, the 'clearance-remodeling-regeneration' sequence refers to a coordinated MQC process in which damaged mitochondria are first segregated and removed through mitochondrial fission and mitophagy, followed by mitochondrial network remodeling and mitochondrial biogenesis to restore mitochondrial mass and function. The present review summarizes the current advances in understanding the molecular mechanisms governing MQC in ALI, with an emphasis on mitophagy, mitochondrial biogenesis and mitochondrial dynamics. It further discusses etiology-dependent MQC patterns and therapeutic challenges to provide a comprehensive and balanced overview of MQC in the context of ALI.

2. Core modules and regulatory mechanisms of MQC

MQC is a fundamental regulatory system that maintains mitochondrial homeostasis and supports cell survival. It is composed of three core modules: Mitophagy, mitochondrial biogenesis and mitochondrial dynamics, which operate in a coordinated rather than independent manner. Under stress conditions, these modules are temporally organized and functionally integrated through shared signaling pathways, including AMPK-PGC-1α signaling, which links mitochondrial biogenesis to energy stress responses, and PINK1/Parkin signaling, which couples mitochondrial damage sensing to mitophagy and network remodeling (16,17). The core components and coordinated regulation of MQC are illustrated in Fig. 1. The present review outlines the basic regulatory features of each MQC module and their coordinated interactions, providing a unified framework for understanding etiology-specific MQC patterns in ALI.

Mitophagy: Selective elimination of damaged mitochondria. Mitophagy is a selective autophagic process that identifies and eliminates dysfunctional mitochondria during cellular stress. Its primary function is to limit the excessive production of ROS and the release of pro-apoptotic signals from damaged mitochondria. Thus, mitophagy prevents the amplification of mitochondrial injury and reduces cellular toxicity (18). Simultaneously, the degradation products generated through mitophagy can be reutilized to support cellular energy metabolism and biosynthesis, rendering mitophagy the first line of defense in the MQC system (19).

Mitophagy is primarily mediated via two complementary pathways: Ubiquitin-dependent and receptor-mediated ubiquitin-independent mechanisms (20). The ubiquitin-dependent pathway is characterized by activation of the PTEN-induced kinase 1 (PINK1)-Parkin axis, and is primarily triggered by mitochondrial depolarization and related damage signals (21,22). By contrast, receptor-mediated mitophagy relies on outer mitochondrial membrane receptors, including BCL2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3), BCL2/adenovirus E1B 19-kDa-interacting protein 3-like (BNIP3L; also known as NIX) and FUN14 domain containing 1 (FUNDC1), which directly interact with LC3 and serve prominent roles under hypoxic and oxidative stress conditions (23,24). These pathways function in a complementary manner depending on the nature and intensity of cellular stress (25).

From a regulatory perspective, mitophagy exhibits pronounced temporal dependence, selectivity and a context-dependent effect. During the early phase of mitochondrial injury, mitophagy is rapidly activated to selectively eliminate severely damaged mitochondria (26). As injury resolves, mitophagy activity gradually declines and becomes coordinated with subsequent mitochondrial biogenesis, forming a continuous 'clearance-regeneration' regulatory sequence (27). Appropriately regulated mitophagy promotes hepatocyte survival and tissue repair, whereas excessive or prolonged activation may result in aberrant degradation of functional mitochondria, leading to metabolic imbalance and exacerbation of liver injury (28).

Notably, mitophagy should not be interpreted as uniformly protective in ALI. The net effect of mitophagy depends on

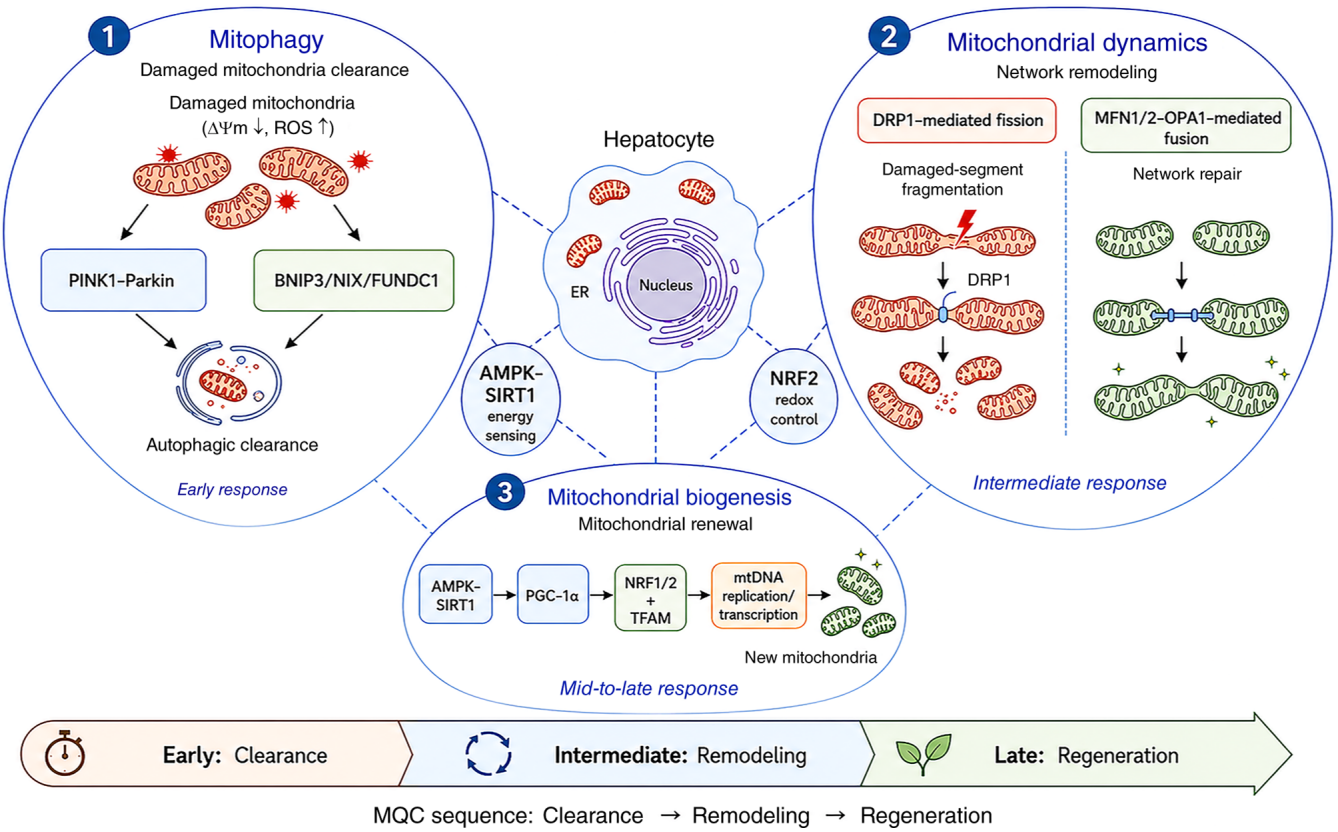

Figure 1. Core framework of MQC in ALI. MQC is an integrated repair network that occurs in hepatocytes during ALI. Three major MQC modules are illustrated in the figure: Mitophagy, mitochondrial dynamics and mitochondrial biogenesis. Mitophagy primarily acts as an early clearance response by removing damaged mitochondria characterized by reduced ΔΨm and increased ROS. This process may be mediated by the ubiquitin-dependent PINK1-Parkin pathway or by receptor-mediated mitophagy involving BNIP3, NIX and FUNDC1. Mitochondrial dynamics represent the remodeling component of MQC. DRP1-mediated fission facilitates the fragmentation and segregation of damaged mitochondrial segments, whereas MFN1/2-OPA1-mediated fusion contributes to mitochondrial network repair and functional complementation. Mitochondrial biogenesis functions as a mid-to-late regenerative response and replenishes mitochondrial mass through the AMPK-SIRT1-PGC-1α-NRF1/2-TFAM axis, which promotes mtDNA replication/transcription and the formation of new mitochondria. AMPK-SIRT1 and NRF2 are representative energy- and redox-sensing regulators that coordinate MQC responses. Collectively, these processes form a temporally organized MQC sequence in ALI: Clearance, remodeling and regeneration. ΔΨm, mitochondrial membrane potential; ALI, acute liver injury; AMPK, AMP-activated protein kinase; BNIP3, BCL2/adenovirus E1B 19-kDa interacting protein 3; DRP1, dynamin-related protein 1; ER, endoplasmic reticulum; FUNDC1, FUN14 domain containing 1; MFN, mitofusin; MQC, mitochondrial quality control; mtDNA, mitochondrial DNA; NIX/BNIP3L, BCL2/adenovirus E1B 19-kDa-interacting protein 3-like; NRF, nuclear factor erythroid 2-related factor; OPA1, optic atrophy 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; SIRT1, sirtuin 1; TFAM, mitochondrial transcription factor A.

injury severity, timing and the capacity of mitochondrial biogenesis to replenish mitochondrial content. Insufficient mitophagy permits the accumulation of damaged mitochondria and amplifies ROS production (13), whereas excessive or prolonged mitophagy may deplete functional mitochondria and aggravate energy failure (29). Therefore, the therapeutic goal should be to restore balanced mitochondrial turnover rather than indiscriminately activate mitophagy.

Mitochondrial biogenesis: Replenishment of mitochondrial content and functional recovery. Mitochondrial biogenesis refers to the generation of new mitochondria through the coordinated regulation of nuclear genes and the mitochondrial genome [mitochondrial DNA (mtDNA)], followed by the integration of newly formed mitochondria into the existing network. As the regenerative arm of MQC, mitochondrial biogenesis serves a critical role in replenishing mitochondrial mass, restoring oxidative phosphorylation capacity, and supporting hepatocyte repair and regeneration (30).

Mitochondrial biogenesis is gradually activated during the intermediate to late stages of ALI, and its activation strength is closely associated with tissue repair capacity (31). The central regulatory axis of mitochondrial biogenesis is organized around peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1α (PGC-1α). PGC-1α cooperates with transcriptional regulators, such as nuclear factor erythroid 2-related factor (NRF)1/2 and mitochondrial transcription factor A (TFAM) to promote the expression of nuclear-encoded mitochondrial proteins, mtDNA replication and mtDNA transcription (32,33). Energy-sensing pathways, including the AMP-activated protein kinase (AMPK)-sirtuin 1 (SIRT1) pathway, modulate PGC-1α activity, thereby tightly coupling cellular metabolic status to mitochondrial regenerative responses (34).

Mitochondrial biogenesis is characterized by clear temporal and stress dependence (35). Its activation typically lags behind mitophagy and proceeds in parallel with hepatocellular recovery (36). Moreover, mitochondrial biogenesis is closely

coordinated with mitophagy and mitochondrial dynamics. Autophagic degradation products, including amino acids, fatty acids and nucleotides, serve as substrates for macromolecular biosynthesis, whereas dynamic remodeling of the mitochondrial network provides a structural framework that promotes the incorporation of newly generated mitochondria (37).

A major unresolved issue is whether mitochondrial biogenesis drives hepatocellular recovery or is merely a secondary marker of tissue repair. Most current evidence is derived from changes in PGC-1α, NRF1/2 or TFAM expression, whereas direct functional validation of newly generated mitochondria remains limited (38,39). Future studies should combine molecular marker detection with analyses of mitochondrial respiratory function, including oxygen consumption and oxidative phosphorylation capacity, mtDNA replication and longitudinal assessment of mitochondrial recovery.

Mitochondrial dynamics: Structural remodeling of the mitochondrial network. Mitochondrial dynamics describe the continuous regulation of mitochondrial morphology and network architecture through the balance between fission and fusion, and represent the structural remodeling component of MQC (40). Their core function is to segregate locally damaged mitochondria through fission, thereby generating substrates for subsequent mitophagy, whereas fusion enables complementation of mitochondrial contents to preserve network integrity and metabolic efficiency (41).

Mitochondrial fission is primarily mediated by dynamin-related protein 1 (DRP1), whereas fusion is coordinated by mitofusin (MFN)1/2 and optic atrophy 1 (42). Under conditions of mitochondrial damage and oxidative stress, the dynamic balance generally shifts toward fission, facilitating the isolation and clearance of dysfunctional mitochondria (17). During the recovery phase, fusion activity progressively increases, supporting the reconstruction of the mitochondrial network and functional compensation. Dysregulation of mitochondrial dynamics may lead to excessive fragmentation or abnormal elongation, thereby amplifying oxidative stress and metabolic dysfunction, and accelerating hepatocellular injury (43).

Although excessive mitochondrial fission is commonly associated with the progression of injury, mitochondrial fragmentation may also represent an adaptive step that segregates damaged mitochondrial segments for mitophagy. Thus, the complete inhibition of fission may be detrimental in certain contexts. The key issue is not whether fission or fusion is beneficial but whether mitochondrial dynamics are appropriately synchronized with mitophagy and biogenesis.

Coordinated regulation of the three core MQC modules. Mitophagy, mitochondrial biogenesis and mitochondrial dynamics form a highly interconnected regulatory network. These modules collectively maintain mitochondrial homeostasis through temporal coordination, functional complementarity and signal integration (44). At a systems level, these modules follow a common regulatory sequence of 'clearance first, remodeling next and regeneration last' (45,46). In the early phase of ALI, mitochondrial dynamics shift toward fission and cooperate with mitophagy to eliminate damaged mitochondria (47). Subsequently, these dynamics progressively favor fusion to remodel the mitochondrial network. During the intermediate to late phases, mitochondrial biogenesis is activated, enabling the generation and integration of new mitochondria and promoting functional recovery (48).

At the signaling level, multiple pathways participate in coordinating these three MQC modules. Among them, AMPK-SIRT1 functions as a central energy-sensing hub that integrates mitophagy activation, dynamic balance adjustment and the initiation of mitochondrial biogenesis (49). NRF2 indirectly modulates mitochondrial dynamics and promotes regenerative responses by alleviating oxidative stress (50). Mitochondrial-nuclear communication may also contribute to the adjustment of MQC activation strength and timing according to the extent of mitochondrial damage (14,51).

Although MQC operates within a unified regulatory framework, its activation patterns exhibit substantial heterogeneity across different ALI etiologies and among distinct hepatocyte subpopulations (52). This heterogeneity directly influences mitochondrial repair efficiency and cell fate decisions, and provides a theoretical basis for subsequent etiology-oriented precision intervention strategies.

3. Etiology-dependent regulation of MQC in ALI

A fundamental manifestation of mitochondrial functional heterogeneity is etiology-dependent regulation. ALI caused by distinct pathogenic factors differs markedly in the nature of the initial insult, mode of mitochondrial damage, injury severity and temporal progression (52,53). These differences directly result in pronounced heterogeneity in activation timing, dominant regulatory pathways and coordination of the three core modules of MQC, namely mitophagy, mitochondrial biogenesis and mitochondrial dynamics (Fig. 2). In the present review, drug-induced liver injury (DILI), IRI and viral ALI were used as representative models to systematically compare etiology-specific MQC response patterns, thereby providing a mechanistic basis for precision-targeted therapeutic interventions.

MQC patterns in DILI. DILI is one of the most common causes of ALI, with acetaminophen (APAP) overdose and injury associated with herbal medicines or dietary supplements being the most common (54). Mitochondrial damage in DILI is direct and dose-dependent. It mainly results from reactive drug metabolites, such as N-acetyl-p-benzoquinone imine, generated during APAP metabolism, which directly interacts with mitochondrial proteins (55,56). These interactions lead to the collapse of mitochondrial membrane potential, excessive ROS production and mtDNA damage. Under these conditions, MQC activation in DILI is characterized by a pronounced context-dependent role of mitophagy, with NRF2 signaling acting as the dominant upstream regulator (57). Reduced NRF2 activity markedly impairs PINK1 expression and delays mitophagy activation in APAP-induced liver injury models, thus resulting in excessive accumulation of damaged mitochondria and the expansion of hepatocellular necrosis (58,59). By contrast, enhanced NRF2 activation promotes mitophagy and mitochondrial biogenesis, thereby improving hepatocyte survival and alleviating tissue injury (60).

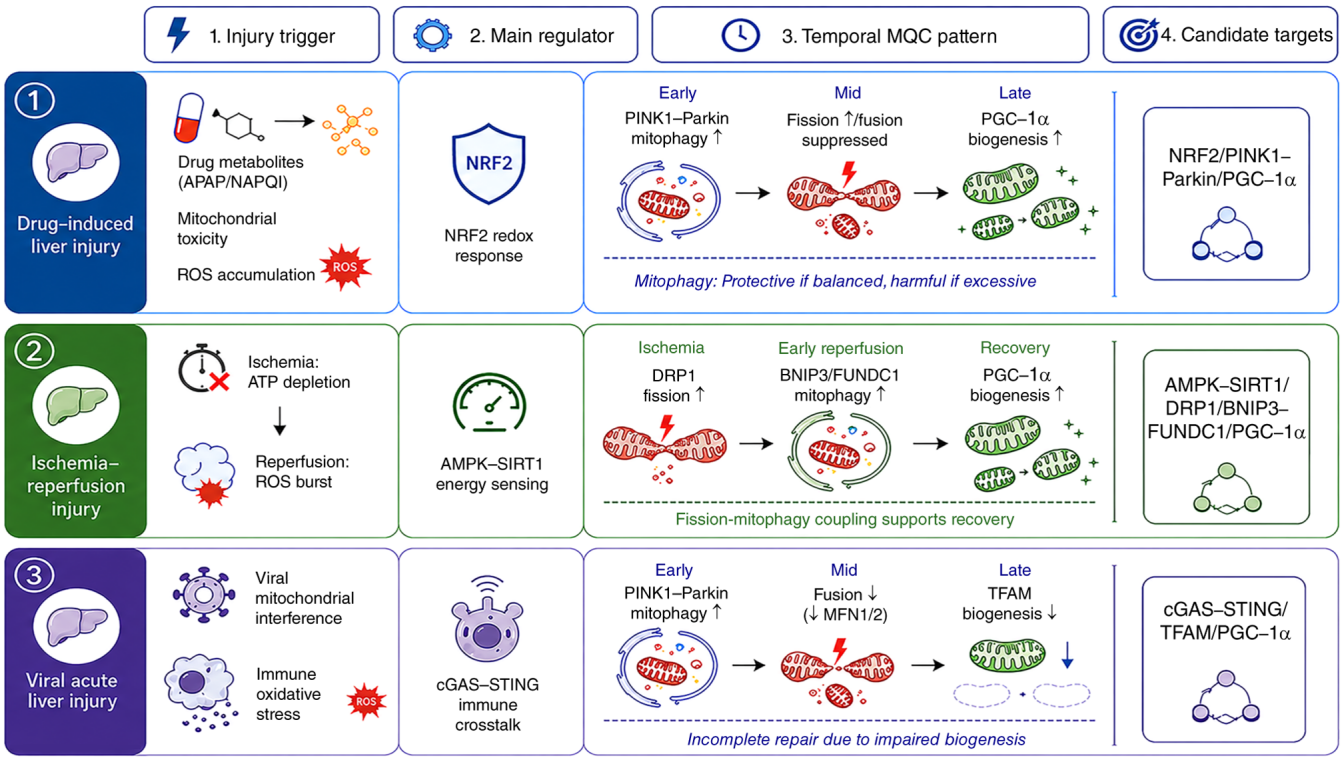

Figure 2. Etiology-dependent patterns of MQC in ALI. This schematic diagram summarizes the etiology-dependent MQC response patterns in three representative forms of ALI: DILI, IRI and viral acute liver injury. In DILI, drug metabolites, such as APAP-derived NAPQI, induce mitochondrial toxicity and the accumulation of ROS. NRF2-mediated redox response represents a major regulatory context, accompanied by early PINK1-Parkin-mediated mitophagy, mid-stage mitochondrial fission with suppressed fusion, and late PGC-1α-associated mitochondrial biogenesis. Mitophagy in DILI is context-dependent; balanced activation may support mitochondrial clearance and hepatocyte protection, whereas excessive or prolonged activation may aggravate mitochondrial depletion and energy failure. In IRI, ischemia-induced ATP depletion, followed by a reperfusion-associated ROS burst, activates AMPK-SIRT1-mediated energy sensing. DRP1-dependent fission, BNIP3/FUNDC1-associated mitophagy and PGC-1α-driven mitochondrial biogenesis are sequentially engaged, and efficient fission-mitophagy coupling supports mitochondrial recovery. In acute viral liver injury, the illustrated pattern is a representative mechanism rather than a universal response across all viral etiologies. Viral mitochondrial interference and immune oxidative stress promote early PINK1-Parkin-associated mitophagy and innate immune crosstalk involving cGAS-STING. However, fusion suppression, reduced MFN1/2 activity and TFAM-related impairment of mitochondrial biogenesis may prevent completion of the clearance-remodeling-regeneration repair sequence. Candidate intervention targets shown in the figure include NRF2, PINK1-Parkin and PGC-1α in DILI; AMPK-SIRT1, DRP1, BNIP3-FUNDC1 and PGC-1α in IRI; and cGAS-STING, TFAM and PGC-1α in viral acute liver injury. APAP, acetaminophen; ALI, acute liver injury; AMPK, AMP-activated protein kinase; BNIP3, BCL2/adenovirus E1B 19-kDa interacting protein 3; cGAS, cyclic GMP-AMP synthase; DILI, drug-induced liver injury; DRP1, dynamin-related protein 1; FUNDC1, FUN14 domain containing 1; IRI, ischemia-reperfusion injury; MFN, mitofusin; MQC, mitochondrial quality control; NAPQI, N-acetyl-p-benzoquinone imine; NRF, nuclear factor erythroid 2-related factor; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; SIRT1, sirtuin 1; STING, stimulator of interferon genes; TFAM, mitochondrial transcription factor A.

MQC activation in DILI generally follows a sequential pattern consisting of early mitophagy activation, intermediate remodeling of mitochondrial dynamics and late induction of mitochondrial biogenesis (46,52). During the early phase after injury, rapid ROS accumulation activates the PINK1-Parkin pathway and NRF2 signaling, inducing mitophagy to eliminate severely damaged mitochondria (61). In the intermediate phase, mitochondrial dynamics shift toward enhanced fission accompanied by suppressed fusion, facilitating further segregation and clearance of dysfunctional mitochondria (47). At later stages, NRF2-driven upregulation of PGC-1α initiates mitochondrial biogenesis, replenishing mitochondrial content and gradually restoring oxidative phosphorylation capacity (33). Mitophagy exhibits the most prominent dual effect in DILI; moderate activation under low-dose exposure is protective, whereas excessive activation under high-dose conditions may result in aberrant degradation of functional mitochondria, leading to energy collapse and aggravated liver injury (62).

MQC patterns in IRI. IRI commonly occurs during liver surgery, transplantation or hemorrhagic shock. Pathophysiologically, it involves energy deprivation during ischemia, followed by an abrupt oxidative burst upon reperfusion (63). Unlike in DILI, mitochondrial damage in IRI is characterized by the coexistence of energy-sensing dysregulation and structural disruption. Accordingly, MQC regulation in IRI is functionally dominated by the AMPK-SIRT1 axis and features a tight coupling between mitochondrial fission and mitophagy (64). Experimental evidence indicates impaired mitophagy, including inhibition of DRP1-Beclin-1-dependent mitophagy, compromises the clearance of damaged mitochondria and exacerbates ROS-mediated hepatocellular injury in ischemia-reperfusion models (65,66). By contrast, activation of the AMPK-SIRT1 pathway accelerates the initiation of mitochondrial biogenesis and facilitates the recovery of cellular ATP levels (67).

MQC activation in IRI follows a continuous sequence consisting of ischemia-associated remodeling of mitochondrial

dynamics, reperfusion-driven mitophagy and recovery-phase mitochondrial biogenesis (64). During the ischemic phase, rapid ATP depletion increases the AMP/ATP ratio and activates AMPK, which phosphorylates DRP1 to promote mitochondrial fission and preemptively segregate vulnerable mitochondria (65). In the early reperfusion phase, massive oxygen influx induces a burst of ROS, and AMPK further activates receptor-mediated mitophagy pathways involving BNIP3, enabling the rapid removal of severely damaged mitochondria (64,65). During the subsequent recovery phase, sustained activation of the AMPK-SIRT1 axis promotes PGC-1α-dependent mitochondrial biogenesis, gradually restoring hepatocellular energy homeostasis (49). Collectively, BNIP3-mediated mitophagy and DRP1-dependent mitochondrial fission constitute the key rate-limiting steps in MQC regulation during IRI, and their coordinated efficiency largely determines injury severity and repair capacity.

MQC patterns in viral ALI. Viral ALI results from hepatotropic viral infections, such as hepatitis A virus and hepatitis E virus, and is characterized by a dual origin of mitochondrial damage: Direct viral interference with mitochondrial structure and function, and secondary amplification driven by immune-mediated inflammation and oxidative stress (68). In this context, MQC regulation is characterized by extensive crosstalk between innate immune signaling and MQC, along with persistent suppression of mitochondrial biogenesis (69).

During viral infection, hepatotropic viruses such as hepatitis A and E viruses consume substantial mitochondrial energy to support viral replication, and viral proteins directly compromise mitochondrial membrane integrity (69,70). Simultaneously, cytokines released by natural killer cells and cytotoxic T lymphocytes promote excessive ROS production, further aggravating mitochondrial injury (71-73). Consequently, MQC activation follows a characteristic pattern consisting of early mitophagy activation, intermediate disruption of mitochondrial dynamics and late-stage impairment of mitochondrial biogenesis (74). In the early phase of infection, virus-induced oxidative stress activates the PINK1-Parkin pathway, thereby promoting mitophagy to eliminate damaged mitochondria (75,76). During the intermediate phase, viral proteins suppress MFN1/2 expression, resulting in impaired mitochondrial fusion and fragmentation of the mitochondrial network (74,77). In the later phase, viral interference with PGC-1α signaling inhibits mitochondrial biogenesis, thereby constraining the hepatocellular repair capacity (78).

At the molecular level, the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING)-PINK1 axis represents a critical intersection between MQC regulation and the innate immune response in viral ALI. mtDNA released from damaged mitochondria activates cGAS-STING signaling, which amplifies inflammatory responses and enhances PINK1 expression and mitophagy activation (79,80). In contrast to DILI and IRI, the sustained suppression of mitochondrial biogenesis is a defining feature of viral ALI. Viral downregulation of TFAM directly impairs mtDNA transcription and replication, restricting the generation of new mitochondria and preventing completion of the MQC 'clearance-regeneration' repair cycle (81). These findings suggest that the disruption of mitochondrial biogenesis and TFAM-related mtDNA maintenance impairs mitochondrial recovery during viral infection. However, whether the direct restoration of TFAM improves hepatocyte survival in viral ALI remains unclear (81,82).

Comparative overview and implications of etiology-specific MQC regulation. Taken together, the aforementioned evidence highlights MQC as a highly adaptive and etiology-dependent regulatory network in ALI. Although mitophagy, mitochondrial biogenesis and mitochondrial dynamics operate within a shared conceptual framework, their relative activation timings, dominant regulatory pathways and degrees of coordination vary substantially across different forms of ALI. In DILI, MQC regulation is largely driven by NRF2 signaling and is characterized by a prominent dual role of mitophagy: Appropriate activation enables completion of the clearance-regeneration cycle, whereas excessive activation exacerbates metabolic collapse (83). In IRI, MQC is predominantly governed by energy-sensing mechanisms centered on the AMPK-SIRT1 axis, with tight coupling between mitochondrial fission and mitophagy, enabling the efficient removal of damaged mitochondria and subsequent bioenergetic recovery (65). By contrast, viral ALI can be distinguished by sustained interference with mitochondrial biogenesis. This pattern is driven by the persistent innate immune activation and viral suppression of mitochondrial transcriptional programs. Consequently, the MQC repair loop remains incomplete despite early induction of mitophagy (81).

These etiology-specific MQC patterns indicate that mitochondrial responses in ALI are not uniform stress reactions but dynamically tuned processes shaped by the nature, intensity and duration of the injurious stimulus. The efficiency of hepatocellular recovery depends not only on the activation of individual MQC modules but also on their coordinated integration into a functional repair sequence. Disruption of this coordination, such as excessive mitophagy without compensatory biogenesis, can shift MQC from a protective to a maladaptive response (14,35). Recognizing MQC as a context-dependent and temporally staged regulatory network provides a mechanistic basis for stratified therapeutic intervention and sets the stage for the targeted modulation of MQC pathways in ALI.

Unresolved controversies and knowledge gaps in MQC regulation during ALI. Several issues in this field remain unresolved. First, the protective vs. maladaptive role of mitophagy remains context-dependent, and the threshold at which mitophagy shifts from mitochondrial repair to depletion remains unclear. Second, mitochondrial fission may facilitate the segregation of damaged mitochondria or promote excessive fragmentation, depending on the timing and severity of injury. Third, increased expression of mitochondrial biogenesis markers does not necessarily indicate functional recovery of mitochondrial respiration. Finally, the findings from APAP-induced ALI, IRI and viral ALI models may not be directly interchangeable. These uncertainties highlight the need for temporally resolved and etiology-specific studies on MQC in ALI. The major etiology-specific MQC patterns in different forms of ALI are summarized in Table I.

Table I. Etiology-specific patterns of MQC in ALI.

ALI type	Main mitochondrial insult	Dominant MQC feature	Key regulatory pathways	Temporal pattern	Major implication	(Refs.)
DILI	Direct mitochondrial toxicity, ROS accumulation, mtDNA damage and loss of mitochondrial membrane potential	Prominent mitophagy activation with context-dependent effects	NRF2, PINK1-Parkin, PGC-1α	Early mitophagy activation, intermediate mitochondrial dynamics remodeling and late mitochondrial biogenesis	Moderate mitophagy is protective, whereas excessive or prolonged mitophagy may aggravate mitochondrial depletion and energy failure	(55,57,58, 62,83)
IRI	Ischemia-induced ATP depletion followed by reperfusion-associated oxidative burst	Tight coupling between mitochondrial fission and mitophagy	AMPK-SIRT1, DRP1, BNIP3, PGC-1α	Ischemia-associated fission, reperfusion-driven mitophagy and recovery-phase biogenesis	Efficient fission-mitophagy coupling promotes damaged mitochondrial clearance, but excessive fission may worsen fragmentation and injury	(63-67)
Viral ALI	Viral interference with mitochondrial function combined with immune-mediated inflammation and oxidative stress	Early mitophagy with impaired mitochondrial biogenesis	cGAS-STING, PINK1-Parkin, TFAM, PGC-1α	Early mitophagy activation, intermediate disruption of dynamics and late suppression of biogenesis	Incomplete clearance-regeneration repair may limit hepatocellular recovery	(68,69,74, 75,79-82)

ALI, acute liver injury; AMPK, AMP-activated protein kinase; BNIP3, BCL2/adenovirus E1B 19-kDa interacting protein 3; cGAS, cyclic GMP-AMP synthase; DILI, drug-induced liver injury; DRP1, dynamin-related protein 1; IRI, ischemia-reperfusion injury; MQC, mitochondrial quality control; mtDNA, mitochondrial DNA; NRF2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; SIRT1, sirtuin 1; STING, stimulator of interferon genes; TFAM, mitochondrial transcription factor A.

4. Therapeutic strategies targeting MQC in ALI

Given the central role of mitochondrial dysfunction in the initiation and progression of ALI, targeting MQC has emerged as a promising strategy for mechanism-based intervention (84). Based on current experimental and translational studies, MQC-targeted therapeutic strategies for ALI can be divided into three major categories. These include small-molecule drugs, natural compounds, and gene- or cell-based therapies combined with emerging bioengineering technologies (85). These approaches operate on distinct nodes of the MQC network, and can serve as complementary opportunities to preserve mitochondrial integrity, enhance hepatocellular resilience and improve liver injury outcomes (52,85). The present review summarizes representative strategies within each category, and discusses their therapeutic potential and translational challenges.

Small-molecule drugs. Small-molecule drugs represent the most extensively investigated class of MQC-targeted interventions in ALI because of their defined molecular targets and translational feasibility (85). A major therapeutic strategy involves enhancing autophagy and mitophagy by modulating the energy-sensing AMPK-mammalian target of rapamycin (mTOR) axis (86). AMPK activation, for example, by metformin, promotes autophagic clearance of damaged mitochondria, whereas inhibition of mTOR signaling by agents such as rapamycin facilitates mitophagy and has demonstrated hepatoprotective effects in experimental models of DILI (87,88). By reinforcing endogenous mitochondrial turnover mechanisms, these agents limit the accumulation of dysfunctional ROS-generating mitochondria and attenuate downstream inflammatory signaling (62). Activation of PINK1-Parkin-mediated mitophagy not only removes compromised mitochondria but also suppresses inflammasome activation in stressed hepatocytes (89).

Beyond mitophagy induction, pharmacological modulation of mitochondrial dynamics has emerged as an important option for MQC-targeted therapy (90). Excessive mitochondrial fission, largely mediated by DRP1, contributes to mitochondrial fragmentation and metabolic failure in ALI (91). Accordingly, DRP1 inhibition by Mdivi-1 has been reported to alleviate cecal ligation and puncture-induced sepsis-associated liver injury, at least in part, by suppressing STING signaling activation in Kupffer cells and attenuating systemic inflammatory responses (92). Conversely, strategies that enhance mitochondrial fusion or stimulate mitochondrial biogenesis can improve cellular bioenergetic capacity. Small molecules that activate SIRT1/PGC-1α-related signaling restore mitochondrial function and promote mitochondrial biogenesis in experimental hepatic IRI (67).

Beyond these canonical pathways, small-molecule modulators of the BCL-2 family of proteins are also being explored for their ability to indirectly trigger mitophagy (93). The inhibition of the anti-apoptotic protein MCL-1 by compounds such as UMI-77 has been reported to induce mitophagy in non-hepatic preclinical models. Although these findings suggest that pharmacological induction of mitophagy is therapeutically relevant, its role in ALI remains unclear (94,95). Collectively, these pharmacological approaches act on distinct but interconnected nodes of the MQC network, including mitophagy induction, dynamic remodeling and mitochondrial regeneration, and converge to preserve mitochondrial homeostasis and reduce hepatocyte death in ALI.

Natural compounds. Naturally derived compounds have attracted increasing attention as modulators of MQC in ALI, largely owing to their pleiotropic biological activities and favorable safety profiles. Several of these compounds exert hepatoprotective effects by simultaneously targeting oxidative stress, mitochondrial turnover and bioenergetic homeostasis, thereby influencing multiple nodes of the MQC network (96).

Plant-derived polyphenols and antioxidants have been the most extensively studied group in this category. Resveratrol, a prototypical polyphenol, has been reported to alleviate experimental liver injury by reducing oxidative stress and inflammatory responses, and inducing SIRT1/p62-mediated mitophagy (97). These findings suggest that resveratrol preserves mitochondrial homeostasis mainly through SIRT1-related mitophagy and redox regulation, although most evidence remains preclinical and model-dependent (97). Similarly, quercetin has been reported to improve acute liver failure by modulating mitophagy-related apoptosis and inflammatory responses through the PPARγ/PGC-1α/NF-κB axis (98). Curcumin has also shown hepatoprotective potential, primarily through antioxidant and anti-inflammatory mechanisms, including the activation of NRF2 signaling and inhibition of NF-κB activation; however, direct evidence linking curcumin to hepatic mitophagy in ALI remains limited (99). By limiting ROS accumulation and facilitating the removal of dysfunctional mitochondria, these compounds help maintain the mitochondrial membrane potential and ATP production in stressed hepatocytes (61).

In addition to phytochemicals, several endogenous molecules and nutritional supplements have been implicated in MQC regulation (100). Melatonin has been reported to attenuate experimental liver IRI by modulating mitochondrial injury-related pathways, supporting its potential role in mitochondrial protection during ALI (101). Coenzyme Q10, a mitochondrial electron carrier and lipid-soluble antioxidant, may theoretically support mitochondrial redox homeostasis and bioenergetic functions, although ALI-specific evidence remains limited (102). Moreover, several natural compounds have been reported to regulate PGC-1α-related mitochondrial biogenesis in non-ALI metabolic models. These findings suggest a link between natural compounds and mitochondrial regeneration; however, their relevance to ALI requires further validation (103,104).

Collectively, natural compounds modulate MQC through their integrated effects on redox homeostasis, mitophagy activation and mitochondrial regeneration. Although most evidence remains at the preclinical level, the multitarget actions of these agents make them attractive complementary candidates for MQC-based intervention strategies for ALI.

Gene- and cell-based therapies and emerging technologies. Beyond conventional pharmacological approaches, gene- and cell-based therapies represent innovative strategies for

targeting MQC in ALI. Emerging bioengineering technologies have further expanded this therapeutic landscape by enabling direct restoration of mitochondrial homeostasis (105).

Gene-based strategies focus on precise manipulation of key regulators that govern mitophagy, mitochondrial biogenesis and responses to oxidative stress. Targeted delivery or overexpression of genes such as PINK1, Parkin, PGC-1α and NRF2 has been shown to enhance mitochondrial clearance, regeneration and antioxidant capacity in preclinical models of ALI (52,83). Conversely, genetic inhibition of maladaptive pathways, including excessive mitochondrial fission and mtDNA-driven inflammatory signaling, can mitigate hepatocellular damage while preserving essential MQC functions. Although still largely experimental, these approaches highlight the potential for directly reprogramming mitochondrial stress responses at the molecular level.

Cell-based therapies provide an additional dimension of MQC modulation by exploiting the regenerative and immunomodulatory properties of stem cells. In particular, mesenchymal stem cells (MSCs) enhance mitochondrial function through paracrine signaling, attenuation of oxidative stress and suppression of inflammation (106). Accumulating evidence has indicated that MSCs and their extracellular vesicles facilitate the transfer of functional mitochondria or mitochondrial components to injured cells, thereby restoring their bioenergetic capacity and enhancing cellular resilience (106,107). This mitochondria-centered repair mechanism represents a unique advantage of cell-based approaches in severe mitochondrial dysfunction.

Emerging bioengineering technologies have expanded the therapeutic landscape by enabling targeted and efficient modulation of MQC at the subcellular level (108). Advances in mitochondrial transplantation, mitochondria-targeted drug delivery systems and nanotechnology-based platforms, such as the transplantation of isolated healthy mitochondria and the use of mitochondria-targeted nanocarriers to deliver antioxidants or other therapeutic agents (109,110), have enabled the selective enhancement of mitochondrial function, suppression of oxidative stress at its source and promotion of network recovery with high spatial precision. Although these technologies remain in the early stages of development, they offer promising solutions to the longstanding challenges related to targeting specificity and therapeutic efficacy.

Collectively, gene- and cell-based interventions and emerging technologies reflect a paradigm shift from indirect modulation to direct restoration of mitochondrial integrity. By reinforcing MQC at the genetic, cellular and subcellular levels, these approaches have a substantial potential to complement existing therapies and enable more precise etiologically adapted treatment strategies for ALI.

Integrative summary of MQC-targeted therapeutic strategies. Therapeutic strategies targeting MQC provide a multifaceted framework for mitigating ALI by directly addressing mitochondrial dysfunction, a central driver of hepatocellular damage. The approaches discussed in the present review, including small-molecule drugs, natural compounds, gene- and cell-based therapies, and emerging bioengineering technologies, converge on the shared objective of preserving or restoring mitochondrial homeostasis in stressed hepatocytes. These strategies can reduce oxidative stress, remove or replace damaged mitochondria, and restore bioenergetic function through coordinated regulation of mitophagy, mitochondrial dynamics and mitochondrial biogenesis.

An effective MQC-targeted intervention is unlikely to depend on the simple activation of mitochondrial turnover. Instead, it requires precise context-dependent modulation according to the etiology of the injury, disease stage and balance among individual MQC modules (52,85). However, whether these strategies can be translated into clinical practice depends on several unresolved issues, including safety, delivery, therapeutic timing, biomarkers and patient heterogeneity. The translational challenges are discussed in detail in the current review.

Translational barriers and clinical challenges of MQC-targeted therapies. Despite encouraging preclinical findings, several barriers have limited the clinical translation of MQC-targeted therapies for ALI. First, most candidate interventions have only been validated in cell-based or animal models; human trials specifically designed to assess MQC modulation are scarce (52,84). Second, safety concerns must be carefully considered because excessive activation or inhibition of MQC may disrupt physiological mitochondrial turnover and impair hepatocyte metabolism (85). Third, efficient delivery to injured hepatocytes remains a challenge, particularly in gene-based strategies, mitochondrial transplantation and nanocarrier systems (108-110). Fourth, the therapeutic window is likely narrow because mitophagy, mitochondrial dynamics and mitochondrial biogenesis exhibit distinct temporal patterns during the progression of ALI. Fifth, reliable biomarkers capable of monitoring mitochondrial damage, mitophagic flux and biogenic activity in patients are still lacking. Finally, patient heterogeneity in etiology, injury severity, comorbidities and baseline mitochondrial function may strongly influence therapeutic responses. These limitations suggest that MQC-targeted therapies require etiologically stratified, time-sensitive and biomarker-guided development before clinical application. Representative MQC-targeted therapeutic candidates, their molecular targets, experimental models and translational statuses are summarized in Table II.

5. Conclusion and future perspectives

Accumulating evidence has established that MQC is a central determinant of hepatocellular fate during ALI. Rather than operating as isolated pathways, mitophagy, mitochondrial biogenesis and mitochondrial dynamics form an integrated regulatory network that regulates mitochondrial turnover, functional recovery and cellular adaptation to acute stress. Dysregulation of this network contributes to mitochondrial dysfunction, metabolic failure and the amplification of liver injury, whereas appropriately tuned MQC responses facilitate hepatocellular repair and liver function restoration.

An emerging concept from previous studies (13,28) is that MQC regulation in ALI is strongly context-dependent. The timing, magnitude and coordination of individual MQC processes vary according to injury etiology, severity and disease stage. While early activation of mitophagy and mitochondrial fission may serve adaptive roles in limiting acute

Table II. Therapeutic candidates targeting MQC in ALI.

Therapeutic category	Representative candidate or strategy	Main molecular target	MQC process affected	Model/evidence base	Status	Major translational limitations	(Refs.)
Small-molecule drugs	Metformin; rapamycin	AMPK-mTOR axis	Autophagy and mitophagy	Rat hepatic ischemia/reperfusion model	Preclinical; clinically approved for other indications	Optimal dose, timing and patient selection remain unclear	(87,88)
	Mdivi-1	DRP1	Mitochondrial fission	CLP-induced sepsis-associated liver injury model	Preclinical	Specificity, safety and long-term effects remain debated	(92)
Natural compounds	Resveratrol	SIRT1/AMPK pathway	Mitophagy and mitochondrial function	LPS-induced inflammatory liver injury model in Gibel carp	Preclinical	Limited bioavailability and uncertain clinical dosing	(97)
	Quercetin; curcumin	NRF2-, PGC-1α- or inflammation-related pathways	Redox regulation, mitophagy and mitochondrial recovery	Experimental acute liver failure and LPS/D-GalN-induced ALI models	Preclinical	Low bioavailability and insufficient human evidence	(98,99)
Endogenous/nutritional compounds	Melatonin	Antioxidant and mitochondrial injury-related pathways	Mitochondrial protection and redox homeostasis	Hepatic IRI model	Preclinical; clinical evidence in ALI remains limited	Lack of ALI-specific clinical validation	(101)
Gene-based therapies	PINK1, Parkin, PGC-1α or NRF2 modulation	Mitophagy, mitochondrial biogenesis and antioxidant response pathways	Direct reinforcement of MQC programs	APAP-induced ALI model and other preclinical liver injury models	Experimental/preclinical	Delivery efficiency, off-target effects and safety concerns	(52,83)
Bioengineering strategies	Mitochondrial transplantation or mitochondria-targeted nanocarriers	Mitochondrial delivery and subcellular targeting	Direct mitochondrial restoration	Murine hepatic IRI model and mitochondria-targeted delivery evidence	Early preclinical research	Delivery specificity, immune response and scalability remain unresolved	(109,110)

ALI, acute liver injury; AMPK, AMP-activated protein kinase; APAP, acetaminophen; CLP, cecal ligation and puncture; D-GalN, D-galactosamine; DRP1, dynamin-related protein 1; IRI, ischemia-reperfusion injury; LPS, lipopolysaccharide; MQC, mitochondrial quality control; mTOR, mammalian target of rapamycin; NRF2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PINK1, PTEN-induced kinase 1; SIRT1, sirtuin 1.

mitochondrial damage, sustained or excessive activation can become maladaptive by exacerbating mitochondrial depletion and energy insufficiency (29). These observations underscore the need for balanced and temporally regulated MQC responses to achieve effective hepatocellular recovery.

Despite these advances, certain limitations of current state-of-the-art methods should be acknowledged. First, most evidence supporting MQC regulation in ALI has been derived from cell-based experiments and animal models, whereas direct evidence from human ALI samples remains limited; this restricts the clinical applicability of the conclusions drawn from preclinical studies. Second, different experimental models of ALI, such as APAP-induced injury, IRI and viral liver injury, differ substantially in terms of injury mechanisms, temporal progression and mitochondrial stress patterns (59,64,68). Therefore, MQC findings from one model cannot be directly generalized to all forms of ALI. Third, current methods for evaluating MQC remain incomplete. A number of studies (35,36,38,39) rely on static markers such as PINK1, Parkin, LC3, PGC-1α, TFAM, DRP1 or MFN1/2; however, these markers do not fully reflect mitophagy flux, mitochondrial biogenesis activity or dynamic mitochondrial network remodeling *in vivo*. Fourth, the dual role of MQC has not been fully clarified. Although moderate mitophagy and mitochondrial fission may remove damaged mitochondria and protect hepatocytes, excessive or prolonged activation may lead to mitochondrial depletion, bioenergetic failure and aggravation of injury. Finally, the lack of reliable biomarkers for mitochondrial damage and MQC status limits patient stratification and prevents the accurate selection of therapeutic timing.

Therefore, future research should move from descriptive pathway analyses to temporally resolved, clinically oriented investigations. Single-cell mitochondrial profiling may help identify hepatocyte subpopulations with distinct MQC states during injury progression and repair. Spatial transcriptomics and proteomics could further clarify how MQC responses differ between necrotic, inflammatory and regenerating regions within injured liver tissue. Additionally, artificial intelligence-assisted biomarker discovery may facilitate the identification of circulating or tissue-based indicators of mitochondrial injury, mitophagy and regenerative capacity. These approaches may provide a basis for precision hepatology, in which MQC-targeted interventions are selected according to the injury etiology, disease stage, biomarker status and patient-specific metabolic background. More clinically relevant animal models, human liver samples and prospective translational studies are required to determine whether MQC modulation can be safely and effectively applied to patients with ALI.

In conclusion, MQC is a dynamic and context-dependent regulatory system that links mitochondrial damage control with hepatocellular repair. A better understanding of its temporal regulation, etiology-specific features and translational limitations is essential for the development of mechanism-based and precision therapeutic strategies for ALI.

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Authors' contributions

ZC conceptualized the study, conducted the investigation, and contributed to writing, reviewing and editing the manuscript. YW contributed to visualization and to writing, reviewing and editing the manuscript. YL performed validation and contributed to writing, reviewing and editing the manuscript. GC contributed to visualization and to writing, reviewing and editing the manuscript. YC and YB conducted the investigation and contributed to writing, reviewing and editing the manuscript. YZ conceptualized the study, administered the project, acquired funding, and contributed to writing, reviewing and editing the manuscript. LZ conceptualized and supervised the study, administered the project, and contributed to writing, reviewing and editing the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of this work.

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Competing interests

The authors declare that they have no competing interests.

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