Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(8): 41721
https://doi.org/10.31083/FBL41721

Review

Metabolic Dysfunction-Associated Steatotic Liver Disease and Mitochondrial Quality Control: From Laboratory to Clinical Practice

Wenkai Fu[1], Junqi Wang[1], Nan Lu[1], Zhijiang Guo[2], Sang-Bing Ong[2], Yong Gao[3], Hao Zhou[4], Xing Chang[5,*], Miao Meng[6,*]

[1]The Third School of Clinical Medicine, Beijing University of Traditional Chinese Medicine, 100029 Beijing, China
[2]Department of Medicine & Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong (CUHK), Hong Kong SAR, China
[3]State Key Laboratory of Traditional Chinese Medicine Syndrome, Science and Technology Innovation Center, Guangzhou University of Chinese Medicine, 510006 Guangzhou, Guangdong, China
[4]Cardiology, Senior Department of Cardiology, PLA General Hospital, 100048 Beijing, China
[5]Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, 100053 Beijing, China
[6]Gastroenterology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, 100053 Beijing, China
*Correspondence: xingchang_tcm@outlook.com (Xing Chang); mengmiao_1020@sina.com (Miao Meng)
Academic Editor: Graham Pawelec
Submitted: 19 May 2025 Revised: 21 July 2025 Accepted: 25 July 2025 Published: 4 August 2026

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) affects more than 1.66 billion people globally. This metabolic disorder shows strong connections with mitochondrial dysfunction and disrupted mitochondrial quality control (MQC) processes. Our review systematically analyzes the molecular mechanisms underlying the relationship between MQC and MASLD development. Research evidence indicates that impaired MQC regulation worsens three key pathological conditions: it intensifies liver fat accumulation, increases oxidative damage, and promotes inflammatory cell death through activating inflammatory signaling pathways, boosting reactive oxygen species generation, and triggering programmed cell death in hepatocytes. Current pharmacological interventions have shown mixed effects. Metformin, resveratrol, and empagliflozin have moderating effects on MQC homeostasis in experimental models, but their clinical application remains limited. The review further predicts two key systemic impacts of MASLD: it amplifies cardiovascular disease risk through links between organ systems, and it highlights the need to develop targeted regulation of the gut microbiota. Three major research challenges require urgent attention: first, clarifying the complex interactions between different MQC pathways; second, establishing clinical effectiveness through human trials; third, bridging the gap between laboratory findings and practical medical interventions. These priorities highlight the need for coordinated multidisciplinary research efforts to address this growing public health challenge.

Keywords: MASLD; MQC; inflammation; oxidative stress; apoptosis

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now widely accepted as an alternative neoterm for Non-alcoholic fatty liver disease (NAFLD). NAFLD is defined as the pathological accumulation of fat in liver cells occurring in non-moderate drinkers. NAFLD's diagnostic criterion involves hepatic steatosis in at least 5% of liver cells, without excessive alcohol intake [1]. Emerging evidence suggests that >96% of patients with NAFLD meet criteria for MASLD; Therefore, the two definitions are used interchangeably [2]. The global prevalence of MASLD in adults is approximately 30%, and as of 2019, it is estimated that there are approximately 1.66 billion cases of MASLD worldwide [3]. The escalating MASLD now constitutes a primary driver of liver transplantation demand. Current transplant registry data show this condition has become the second most common transplant indication in the United States [4]. MASLD demonstrates a spectrum of pathological progression, ranging from isolated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH) with varying degrees of liver fibrosis that may progress to cirrhosis [5,6]. The surge in obesity rates, type 2 diabetes, and metabolic syndrome across the globe has led to a nearly 50% uptick in the prevalence of MASH, solidifying its status as the leading cause of chronic liver issues [7].

Mitochondrial dysfunction is central to MASLD development, as it disrupts lipid metabolism, amplifies oxidative stress, and triggers inflammatory cascades. Mitochondrial quality control, encompassing mitophagy, dynamics, biogenesis, and the mitochondrial unfolded protein response (UPR^{mt}), is vital in preserving the liver's metabolic balance [8]. Interruption of the mitochondrial quality control (MQC) process induces three interrelated metabolic dysfunctions: fatty acid oxidation defects, reactive oxygen species (ROS) overproduction, and programmed cell death. Together, these three mechanisms constitute the core pathophysiological triad that drives MASLD progression. However, a comprehensive synthesis of how MQC pathways interact within the MASLD microenvironment is lacking, directly obstructs the development of targeted therapies.

This review systematically elucidates the interaction between mitochondrial quality control mechanisms and MASLD progression. We focus on molecular regulators of mitophagy, fusion/fission kinetics, mitochondrial biogenesis, and UPR^{mt} signaling, while summarizing the drugs that regulate these pathways. By integrating preclinical and clinical insights, we aim to identify novel therapeutic strategies to restore mitochondrial homeostasis in MASLD.

2. Pathogenic Mechanisms of Nonalcoholic Fatty Liver Disease

The development of MASLD stems from the intricate interactions among various metabolic disruptions. Clinical studies have identified a variety of risk factors, including type 2 diabetes, obesity, and metabolic syndrome [9]. The condition specifically includes dyslipidemia, abdominal obesity, and hypertension. Epidemiological analyses show that these determinants show significant demographic differences, particularly in terms of age stratification, gender differences, and racial propensity [4]. The prevailing "multiple-hit" hypothesis [10] is that lifestyle factors, genetic predisposition, adipose tissue dysfunction, insulin resistance, lipidosis, the inflammatory cascade, oxidative stress, innate immune dysregulation, and gut microbiota dysbiosis play a synergistic role in MASLD [11]. Crucially, mitochondrial dysfunction emerging from these interconnected pathways occupies a central role in MASLD pathogenesis.

2.1 Inflammatory Injury

The development of MASLD is intrinsically linked to systemic proinflammatory states [12]. Hepatic triglyceride (TG) deposition represents the primary pathological manifestation of MASLD [13], this lipid abnormality predominantly occurs in patients with obesity, insulin resistance, type 2 diabetes mellitus, and dyslipidemia [3]. Under insulin-resistant conditions, excessive free fatty acids (FFAs) and lipid metabolites are mobilized [14], precipitating ectopic lipid deposition and lipotoxicity. These processes trigger ROS generation, oxidative stress, and inflammatory cascades. The development of MASLD engages multiple inflammatory injury mechanisms mediated by interconnected immune signaling pathways, primarily involving inflammasome activation, dysregulation of cytokines, adipokines, chemokines, and immune cell phenotypic alterations.

Toxins released by liver cells damaged by fat, like High Mobility Group Box 1 (HMGB1), and molecules associated with pathogens, initiate an immune response, causing immune cells to flood in, all thanks to the detection of these patterns by the body's special receptors [15,16]. The inflammasome is central to MASLD development, triggering the proteolytic processing of pro-IL-1β and pro-IL-18, thus intensifying inflammation and liver cell injury [16]. The natural substance tryptanthrin (TPR) has been shown to inhibit NOD-like receptor family pyrin domain containing 3 (NLRP3)-induced production of IL-1β and caspase-1 and regulate the progression of MASH [17]. Damaged liver cells activate the NF-κB signaling pathway through two mechanisms. First, this activation triggers increased production of inflammatory signaling molecules (e.g., IL-6, CCL2, CCL5). Second, it stimulates excessive secretion of chemotactic proteins (e.g., CXCR3 ligands). These molecular events collectively amplify liver tissue damage through three pathological pathways: sustained inflammation, immune cell infiltration, and cellular stress responses [18,19] (Fig. 1). In the downstream signaling of inflammasome, the substrate gasdermin-D of inflammatory caspase induces hepatocyte pyroptosis [20], establishing a pathogenic cycle.

Kupffer cells (KCs) are macrophages of the liver that are closely associated with inflammation regulation [21]. They have experienced a decrease in number among MASLD/MASH patients and failed to proliferate during the progression of MASH [22]. KC activation through endogenous or exogenous receptors by damage associated molecular patterns (DAMPs) or lipid metabolites enhances transcription of activator protein-1 (AP-1) and proinflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) [23], driving inflammatory responses, hepatocellular fibrosis, and steatosis (Fig. 1). Macrophage polarization and metabolic reprogramming constitute two central drivers of MASH progression. Recent mechanistic studies have identified transmembrane protein 173 (STING) signaling activation and retinoid-related orphan nuclear receptors (RORα) overexpression as novel regulatory nodes in this pathogenic network [23,24]. Concurrently, T helper cell 17 (Th17) lymphocytes and neutrophils critically modulate inflammatory and fibrotic processes in MASH, with neutrophils influencing fibrotic resolution through macrophage polarization [11].

Notably, MASLD-associated inflammatory damage is closely related to intestinal dysbiosis, with significant increases in Firmicutes and Proteobacteria [25]. Gut microbiota not only modulates hepatic nutrient metabolism but also regulates liver inflammation via Toll-like receptor (TLR) ligand signaling, stimulating hepatocyte production of proinflammatory cytokines [26] (Fig. 1). In addition, damage to the intestinal mucosal barrier in patients with MASLD promotes microbial translocation into the systemic circulation, leading to chronic inflammation [27]. A recent study has found that the theabrownin extracted from Qingzhuan tea (QTB) can regulate intestinal flora to prevent steatosis induced by a high-fat diet [28]. Moreover, the traditional Chinese medicine Bi Xie Fen Qing Yin can reduce kidney inflammation in mice by regulating the intestinal flora [29].

2.2 Oxidative Stress

Redox dysregulation, termed oxidative stress, arises from ROS overproduction relative to antioxidant capacity

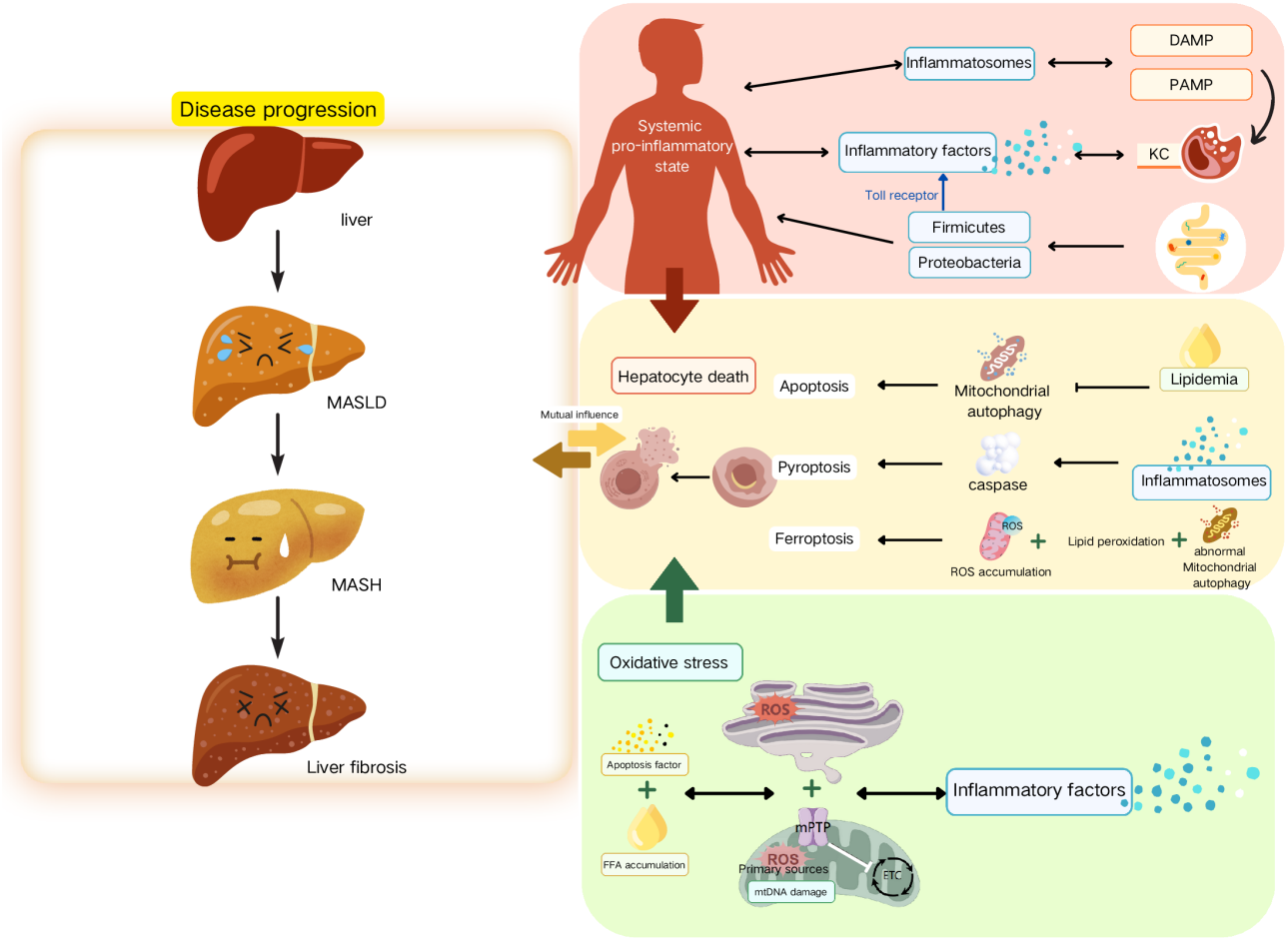

Fig. 1. The onset and progression of metabolic dysfunction-associated steatotic liver disease (MASLD) are closely related to systemic inflammatory state, oxidative stress and hepatocyte death. The systemic inflammatory response is related to inflammatory cells, inflammatory mediators, and the gut microbiota. Oxidative stress mainly includes mitochondrial stress and endoplasmic reticulum (ER) stress. These processes, in turn, can lead to hepatocyte death, which interacts with the MASLD process. MASH, metabolic dysfunction-associated steatohepatitis. All figures were created with canva.com.

[30]. It is both a key component of the "multiple blows" theory and a central driver of MASLD progression [31]. Under oxidative stress, mitochondrial ATP synthesis efficiency is impaired, while excessive ROS accumulation leads to disruption of mitochondrial interactions with the endoplasmic reticulum (ER) [32], accelerating apoptotic cascades. ROS primarily originates from the mitochondrial electron transport chain (ETC) and is linked to the NADPH oxidase (NOX) enzyme [33]. Through the transfer of a single electron from NADPH to molecular oxygen, NOX generates superoxide anions in the mitochondria, with the resulting ROS primarily present in hepatocytes [34,35].

In MASLD patients, oxidative stress mechanisms primarily involve mitochondrial dysfunction, lipid peroxidation, and ER stress. ROS serve not only as biomarkers of oxidative stress [36], but also as potent inflammatory mediators [37,38]. They directly impair mitochondrial respiratory chain function, suppress energy metabolism, and compromise antioxidant systems [39,40]. Excessive ROS generation induces pathological opening of mitochondrial permeability transition pores (mPTPs), inhibits ETC complexes, and reduces mitochondrial membrane potential ($\Delta\Psi m$), culminating in ATP synthesis failure. Concurrently, the release of apoptotic factors activates caspase-dependent apoptotic proteins [41], triggering hepatocyte apoptosis [42] (Fig. 1). Mechanistically, diet-induced MASLD murine models demonstrate that reduced Solute Carrier Family 25 Member 3 (*SLC25A3*) expression impairs mitochondrial copper homeostasis, provoking ETC electron leakage and excessive ROS generation [43].

High-fat diet-induced MASLD exhibits characteristic features including intracellular lipid accumulation, mitochondrial ROS overproduction, and hepatocyte apoptosis [44]. Elevated FFAs exacerbate β-oxidation impairment and mitochondrial dysfunction, while directly or indirectly inducing mitochondrial DNA oxidative damage and ROS amplification [36,45,46]. These processes potentiate lipid peroxidation, upregulate hepatic CC-chemokine ex-

pression, promote C-C chemokine receptor type 5 (CCR5+) cell infiltration, and activate myofibroblasts, collectively driving progressive hepatic fibrosis [47]. Oxidative stress further activates proinflammatory signaling cascades (e.g., NRF2, AP-1, NF-κB, PPARα) [48,49,50,51,52], creating a cycle of inflammation and hepatocyte injury (Fig. 1). However, research indicates that prolonged peroxisome proliferator-activated receptor alpha (PPARα) pathway stimulation can improve mitochondrial fatty acid breakdown and diminish ROS, thus easing MASLD [53]. Inflammatory mediators induce NOX activation, generating radical species that exacerbate oxidative stress [54]. Remarkably, elafibranor, a PPAR-α/δ dual activator, suppresses the synthesis of pro-inflammatory (IL-1β, TNF-α) and profibrotic (TGF-β) factors, thereby significantly mitigating MASH [55].

ER stress activates the UPR to restore proteostasis [56]. The tripartite UPR sensors (PERK, IRE1α, ATF6) orchestrate adaptive responses through autophosphorylation, with persistent activation promoting apoptosis [57]. Protein kinase RNA–like endoplasmic reticulum kinase (PERK) activation temporarily hinders overall protein synthesis and facilitates the specific production of Activating Transcription Factor 4 (ATF4) via eukaryotic initiation factor 2α (eIF2α) phosphorylation [58]. ATF6 upregulates X-box binding protein 1 (XBP1), which mediates inflammatory responses via JNK signaling. Elevated forkhead box A3 (FOXA3) has been shown to exacerbate MASLD progression through ER stress potentiation in murine models [59], collectively underscoring the critical role of ER stress in MASLD pathogenesis.

2.3 Hepatocyte Death

The progression from MASLD to MASH and liver fibrosis is a pathological process where hepatocyte death is not just the end result of liver damage, but also a key factor propelling the disease's harmful progression. When the liver is exposed to free fatty acids, cholesterol overload and oxidative stress for a long time, mitochondria, as the core hubs of energy metabolism and cell fate decision-making, bear the brunt of the damage [60], the MQC network was significantly dysregulated, and lipotoxicity inhibited receptor-mediated mitophagy such as PTEN-induced putative kinase 1 (PINK1)/Parkin pathway and B-cell leukemia/lymphoma 2/adenovirus E1B 19 kDa interacting protein 3-like (BNIP3/NIX), resulting in functionally defective mitochondrial accumulation. At the same time, dynamin-related protein 1 (DRP1)-mediated hyperdivision and mitochondrial fusion protein 2 (MFN2)/optic atrophy 1 (OPA1)-mediated fusion disorder lead to mitochondrial fragmentation, which further weakens their functional compensatory ability [61]; although early Peroxisome proliferator-activated receptors-γ (PPARγ)/peroxisome proliferator-activated receptor gamma co-activator-1 alpha gene (*PGC-1*α) pathway may be compensatory upregulation of biogenesis [62], chronic inflammatory factors such as TNF-α ultimately inhibit new mitochondrial production.

The dysfunction of MQC directly triggers multimodal hepatocyte death. Apoptosis, the primary pathway of programmed cell death under physiological conditions, is triggered by two distinct mechanisms: the intrinsic pathway (mitochondrial or Bcl-2-regulated pathway) and the extrinsic pathway (death receptor pathway). The intrinsic pathway is activated by intracellular stressors such as growth factor deprivation, DNA damage, ER stress, excessive ROS, replication stress, cytoskeletal alterations, or mitotic defects [63]. This pathway relies on the intricate interplay between pro-apoptotic and anti-apoptotic members of the B-cell lymphoma-2 (BCL-2) protein family, which regulate mitochondrial outer membrane permeabilization (MOMP) to initiate apoptosis [64,65]. The extrinsic pathway is initiated by ligand binding to cell surface death receptors (e.g., Fas, TNFR1), leading to the recruitment of adaptor proteins via death domains and formation of the death-inducing signaling complex (DISC). The DISC recruits and activates pro-caspase-8, subsequently cleaves downstream effector caspases to execute apoptosis. Both excessive mitochondrial division and insufficient fusion can lead to mitochondrial fragmentation during apoptosis. In the absence of mitophagy, PINK1/Parkin can promote apoptosis through non-BAX pathways, the ubiquitination of outer mitochondrial membrane (OMM) by Ubiquitin-proteasome system (UPS) promotes the release of cytochrome C, directly activates autophagy receptors, upregulates mitochondrial autophagy, and inhibits apoptosis [66].

Pyroptosis represents a pathologically distinct mode of inflammatory hepatocyte death in MASH, requiring caspase activation and triggering downstream inflammatory cascades. Current research outlines two distinct ways of triggering activation: the first, known as the canonical route, hinges on the activation of caspase-1 via NLRP1, NLRP3, NLRC4, and AIM2 inflammasomes, which then leads to the maturation of IL-1β. DRP1-mediated excessive mitochondrial fission has been reported to contribute to the activation of caspase-1 and NLRP3 inflammasomes, which may be related to mitochondrial dysfunction-induced increased ROS [67,68]. ROS is also an important mediator that promotes hepatocyte necroptosis when mitochondrial autophagy is impaired [69]. Moreover, dysregulation between inflammasome and mitochondrial autophagy pathways may lead to pathological inflammatory responses, which can further aggravate mitochondrial damage and pyroptosis [70].

Ferroptosis is an iron-dependent regulation of cell death characterized by iron overload, lipid peroxidation, ROS accumulation, and plasma membrane rupture. ROS and ATP produced by mitochondria are key substances that regulate the ferroptosis process. Nuclear factor erythroid-2 related factor 2 (NRF2) is a key player in the game of

mitochondrial maintenance. It boosts mitochondrial fusion protein 2 (MFN2) protein levels, fostering mitochondrial fusion while squashing fission, and acts like a cheerleader for new mitochondria to join the party. But yank out NRF2, and you're looking at a surge in ferroptosis [71], in addition, when mitochondria fuse, a buildup of ROS and fatty acids can trigger lipid peroxidation, leading to ferroptosis [72]. Meanwhile, mitochondrial autophagy has a double-edged sword in managing iron death. Mangled or malfunctioning mitochondria dump ROS and some pro-apoptotic factors that can kickstart the iron death process. When mitochondrial autophagy removes abnormal mitochondria, iron death is inhibited [73]. Therefore, MQC plays a central role in the regulation of ferroptosis, and in-depth exploration of its mechanism of action will provide new insights into cell fate and disease progression.

In conclusion, hepatocyte death is by no means a passive outcome, but a key turning point and amplifier in the pathological network of MASLD/MASH—lipotoxicity induces mitochondrial function collapse by destroying MQC, and then activates the three death pathways of apoptosis, pyroptosis and ferroptosis, and the DAMPs released by dead cells and inflammatory cells strongly drive the process of inflammatory infiltration and fibrosis, which further aggravates lipotoxic stress and mitochondrial damage, forming a vicious circle, which is closely related to the process of MQC.

3. Physiological Regulation and Therapeutic Targets of Mitochondrial Quality Control

As the cellular powerhouse, mitochondria play a pivotal role in maintaining cellular homeostasis and vital biological processes [74]. The cells possess a series of complex quality control mechanisms to ensure the proper functioning of mitochondria, which can be categorized into organelle-level regulation and molecular-level regulation [75]. Mitochondrial quality control systems primarily consist of four coordinated mechanisms: mitophagy, mitochondrial biogenesis, mitochondrial dynamics, and the mitochondrial unfolded protein response [8,76]. These coordinated processes maintain mitochondrial structure and function.

3.1 Mitophagy

Mitophagy plays a critical role in maintaining human health, delaying aging-related neurodegenerative diseases, and regulating processes such as inflammation, metabolic transitions, and cellular reprogramming, dysregulated mitophagy can contribute to disease progression [77,78,79]. As a cytoprotective mechanism, mitophagy eliminates superfluous or dysfunctional mitochondria and fine-tunes mitochondrial quantity to balance intracellular homeostasis. In humans, mitophagy is primarily mediated by the PINK1/Parkin, BNIP3/NIX, and FUN14 domain containing 1 (FUNDC1) pathways [80].

3.1.1 PINK1/Parkin Pathway

3.1.1.1 Physiological Mechanism. The PINK1/Parkin Pathway is the earliest identified mitophagy pathway [81]. Upon mitochondrial injury or dysfunction, membrane depolarization triggers PINK1 accumulation on the OMM [82]. Stabilized PINK1 undergoes autophosphorylation at Ser228 for activation [83,84]. Subsequently, PINK1 phosphorylates MFN2 at Thr111 and Ser442, recruiting Parkin to the OMM [85]. Alternatively, PINK1 phosphorylates ubiquitin at Ser65 on OMM proteins to promote Parkin recruitment [86]. Parkin, originally confined to the mitochondria, becomes activated through PINK1's phosphorylation at Ser65 and ubiquitinated phosphoamino acids, initiating substrate ubiquitination and amplifying a feedforward recruitment loop. Parkin ubiquitinates OMM proteins, which are recognized by mitophagy adaptors (e.g., p62, NBR1, HDAC6), facilitating light chain 3 (LC3) recruitment and autophagosome formation [87,88]. Ubiquitin-specific protease 8 (USP8) selectively removes ubiquitin from Parkin at Lys6, enhancing Parkin translocation to depolarized mitochondria and promoting mitophagy [89,90]. Conversely, USP15 and USP30 counteract mitophagy by reversing ubiquitination [91]. Autophosphorylation of PINK1 at Ser228 and Ser402 is essential for ubiquitin recognition [92]. Additional receptors, including SQSTM1/p62, NDP52, OPTN, and TNFα/Miz1, further enhance PINK1/Parkin-mediated mitophagy [93,94,95,96] (Fig. 2).

3.1.1.2 Pathological Targets. During Parkin activation, PINK1 directly phosphorylates Parkin at Ser65 [97], generating pSer65-ubiquitin that resists deubiquitinating enzymes [98]. Phosphatase and tensin homologue (PTEN)-L protein antagonizes pSer65-ubiquitin formation through its phosphatase activity, inhibiting PINK1-dependent Parkin recruitment and mitophagy [99]. Experimental studies have shown that penicillium-derived neosesquiterpenoids attenuate MASLD-associated lipid accumulation through coordinated mitochondrial function. These reagents promote ATP synthesis, stabilize membrane potential, reduce oxidative stress, and restore mitochondrial structure. Mechanistically, they activate the PINK1/Parkin pathway to upregulate mitochondrial quality control proteins and mitophagy markers [100]. In high-fat diet-induced MASLD mice, PINK1 and Parkin expression is significantly downregulated, accompanied by mitochondrial apoptosis pathway activation and mPTP opening [101]. Type 2 diabetic patients exhibit reduced PINK1 and Parkin levels, which are reversed by metformin, restoring ETC complex levels and enhancing adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) activation and mitophagy [102]. It has been found that atractyloside can promote AMPK activation, reduce mTOR activity, and finally promote autophagosome formation and alleviate hepatic steatosis in mice [103].

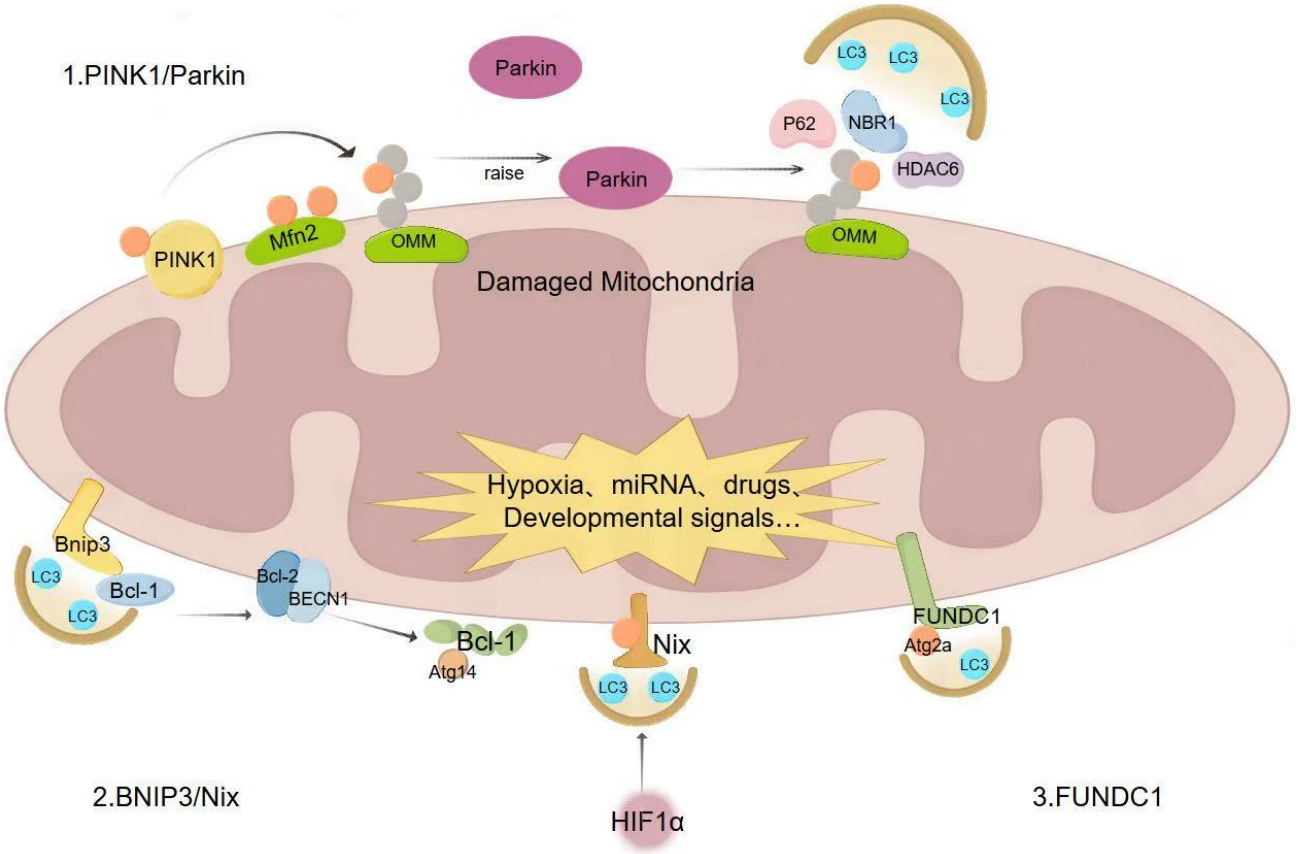

Fig. 2. The process of mitophagy in mitochondrial quality control. The primary pathway for mitophagy in mammalian cells is mediated by three pathways. PINK1/Parkin Pathway can occur in the brace mitochondria or damaged mitochondria, accomplished by phosphorylation and ubiquitination of outer mitochondrial membrane (OMM) proteins; Both BNIP3/NIX and FUNDC1 pathways occur due to instability such as hypoxia, miRNA, and pharmacological modulation. Eventually form the autophagosomes. PINK1, PTEN-induced putative kinase 1; BNIP3/NIX, B-cell leukemia/lymphoma 2/adenovirus E1B 19 kDa interacting protein 3-like; FUNDC1, FUN14 domain containing 1; HIFα, hypoxia-inducible factor α; BECN1, beclin1; MFN2, mitochondrial fusion protein 2; NBR1, NBR1 Autophagy Cargo Receptor; HDAC6, histone deacetylase 6; LC3, light chain; Atg2a, autophagy related protein 2a.

3.1.2 BNIP3/NIX Pathway

3.1.2.1 Physiological Mechanism. Both BNIP3 and NIX are anchored to the OMM, share a non-canonical BH3-only domain and act as mitophagy receptors. Under hypoxia, BNIP3 induces mitophagy via two pathways: (1) Its BH3 domain competitively binds BCL-2 to disrupt the BCL2-BECN1 complex, releasing Beclin-1 to activate mitophagy [104,105]; (2) Its N-terminal LC3-interacting region (LIR) binds Atg8/LC3 to directly recruit autophagosomes [106, 107]. Beyond hypoxia, BNIP3 expression is regulated by cellular stressors, microRNAs (miR-347, miR-30, miR-302/367, miR-133a), pharmacological agents, DNA methylation, and developmental signals [108] (Fig. 2).

3.1.2.2 Pathological Targets. Iron chelator DFP induces robust PINK1/Parkin-independent mitophagy, demonstrating that OMM protein-NIX interactions drive mitophagy [109]. The BNIP3/NIX pathway may intersect with ferroptosis: BNIP3/NIX double-knockout cells exhibit elevated mitochondrial ROS, activating the NRF2 antioxidant pathway while increasing ferroptosis susceptibility [110]. Sirtuin family members (e.g., SIRT1, SIRT3) critically modulate MASLD progression by regulating inflammation, oxidative stress, apoptosis, autophagy, and mitochondrial biogenesis [111]. Sirtuin1 (SIRT1) and SIRT3 enhance Beclin-1 and LC3II expression, prolonging autophagosome activity [112]. Resveratrol and its derivatives alleviate MASLD by activating SIRT1, SIRT3, and PINK1 to stimulate mitophagy [113,114].

3.1.3 FUNDC1 Pathway

3.1.3.1 Physiological Mechanism. FUNDC1 mediates mitochondrial dynamics and quality control by coupling mitochondrial fission, fusion, and mitophagy [115]. Under hypoxia, dephosphorylation of FUNDC1 at Ser13 strengthens its interaction with LC3, enhancing mitophagy. FUNDC1 anchors Optic Atrophy 1 (OPA1) to the inner OMM surface via lysine residue Lys70. Stress-induced OPA1 degrada-

tion or cleavage promotes mitochondrial fission and triggers mitophagy [116]. FUNDC1 also interacts with autophagic protein Autophagy-related protein 2 homolog A (ATG2A), facilitating autophagosome elongation and closure [117] (Fig. 2).

3.1.3.2 Pathological Targets. A "seesaw-like model" clarifies interactions among DRP1, OPA1, and FUNDC1: FUNDC1 binds OPA1 under normal conditions but recruits DRP1 to mitochondria during stress, promoting fission and mitophagy [116]. In hepatic fibrosis, FUNDC1 recruits mitochondrial Glutathione Peroxidase 4 (GPX4) to activate mitophagy, leading to GPX4 degradation and ferroptosis [118]. Both FUNDC1 and BNIP3L are regulated by microRNAs [119]. Artesunate inhibits actin filament associated protein 1 Like 2 gene (*AFAP1L2*) expression and SRC/FUNDC1 phosphorylation, promoting FUNDC1-mediated LC3 recruitment and mitophagy [120], and *in vitro* experiments, A was found to modulate NLRP3 inflammasomes in MASLD, inhibiting lipid accumulation and inflammation [121]. Empagliflozin protects cells through AMPKα1/ULK1-mediated, FUNDC1-dependent mitophagy activation [122,123].

3.2 Mitochondrial Dynamics

Mitochondrial dynamics, the process by which mitochondria maintain their morphology, quantity, and functional equilibrium through continuous fission and fusion, play a pivotal role in cellular energy metabolism, oxidative stress regulation, apoptosis, and intracellular signaling [124].

3.2.1 Mitochondrial Fusion

3.2.1.1 Physiological Mechanism. In mammalian cells, mitochondrial fusion is mediated by MFN1/2 and OPA1, which regulate OMM and inner mitochondrial membrane (IMM) fusion, respectively [125,126]. The process of mitochondrial merging is divided into a two-phase sequence: outer mitochondrial membrane union, followed by inner mitochondrial membrane union.

For OMM fusion, MFN1/2 proteins tether opposing mitochondria via their HR2-domains, forming a SNARE-like tethering complex [127,128,129]. This tethering activity depends on GTP hydrolysis [130,131]. MFN1 exhibits stronger GTPase activity in its G-HB1 domain compared to MFN2, with MFN1 predominantly driving GTP hydrolysis [132]. GTP binding triggers conformational changes in MFN proteins from a folded to an upright state, enabling G-domain dimerization between opposing OMM-bound MFNs to complete tethering [133]. MFN2 forms homotypic (MFN2-MFN2 or MFN1-MFN1) or heterotypic (MFN1-MFN2) oligomers at the OMM [61,134]. MFN1-MFN2 heterotypic complexes demonstrate superior fusion efficiency, likely due to GTP loading and hydrolysis dynamics [132]. Following GTP hydrolysis, the G-domains and HB1 domain of trans-MFN dimers adopt a closed conformation, pulling OMMs into proximity for membrane merger [133]. Moreover, MFN2 enhances the direct contact between the ER and mitochondria [135]. During GTP hydrolysis, the N-terminal cytoplasmic domain of the dynamin-like protein ATL forms trans-dimers, pulling adjacent ER membranes closer for fusion via its three-helix bundle (3HB) [136,137] (Fig. 3). OPA1 mediates IMM fusion through homotypic (OPA1-OPA1) or heterotypic (OPA1-cardiolipin) complexes formed post-OMM fusion [138,139]. OPA1 comes in two forms: the lengthy L-OPA1 variant and the shorter S-OPA1 version, both resulting from the enzymatic breakdown of a protein. Similarities in the MGD domains of S-OPA1 and the yeast protein Mgm1 point to a shared function in the IMM membrane fusion process [139]. OPA1, a GTPase, shapes IMM cristae; its loss causes mitochondrial fragmentation and cristae disorganization [140]. Mgm1/OPA1 assembly induces membrane curvature to form unstable cristae tips. Contact between opposing tips initiates lipid mixing and pore expansion for IMM fusion [133]. Cardiolipin is critical but its exact role remains unclear (Fig. 3).

3.2.1.2 Pathological Targets. Moderate mitochondrial fusion protects against mitophagy during nutrient stress, while excessive fusion suppresses mitophagy [141]. High-fat diets reduce hepatic MFN1 expression, correlating with MASH progression [142]. Reduced MFN2 levels observed in MASH patients and murine models exacerbate disease by impairing phosphatidylserine (PS) transfer to mitochondria, promoting phospholipid biosynthesis and ER stress. OPA1 downregulation in high-fat diet-fed mice is reversed by liraglutide treatment [60]. Bitter melon extract and salvianolic acid B upregulate MFN1/MFN2 expression, mitigating oxidative stress and hepatocyte death to alleviate hepatic inflammation and steatosis [143,144]. The antidiabetic drug pioglitazone enhances OPA1 and MFN2 expression while suppressing DRP1, protecting mitochondrial integrity [145].

3.2.2 Mitochondrial Fission

3.2.2.1 Physiological Mechanism. Mitochondrial fission occurs in response to oxidative stress-induced damage, segregating impaired mitochondria from healthy ones [146, 147]. This process is regulated by DRP1 and its receptors, including fission 1 (FIS1), mitochondrial fission factor (MFF), mitochondrial dynamics proteins of 49 kDa (MID49), and MID51 [148,149]. Under fission signals, cytosolic DRP1 translocates to the OMM, where it binds to receptor proteins and assembles into GTP-dependent higher-order complexes that constrict and sever mitochondria [149,150]. Among these receptors, MFF and MID proteins exhibit stronger interactions with DRP1 [151,152], while FIS1 and MFF independently recruit and oligomerize DRP1 at the OMM, with MFF playing a dominant

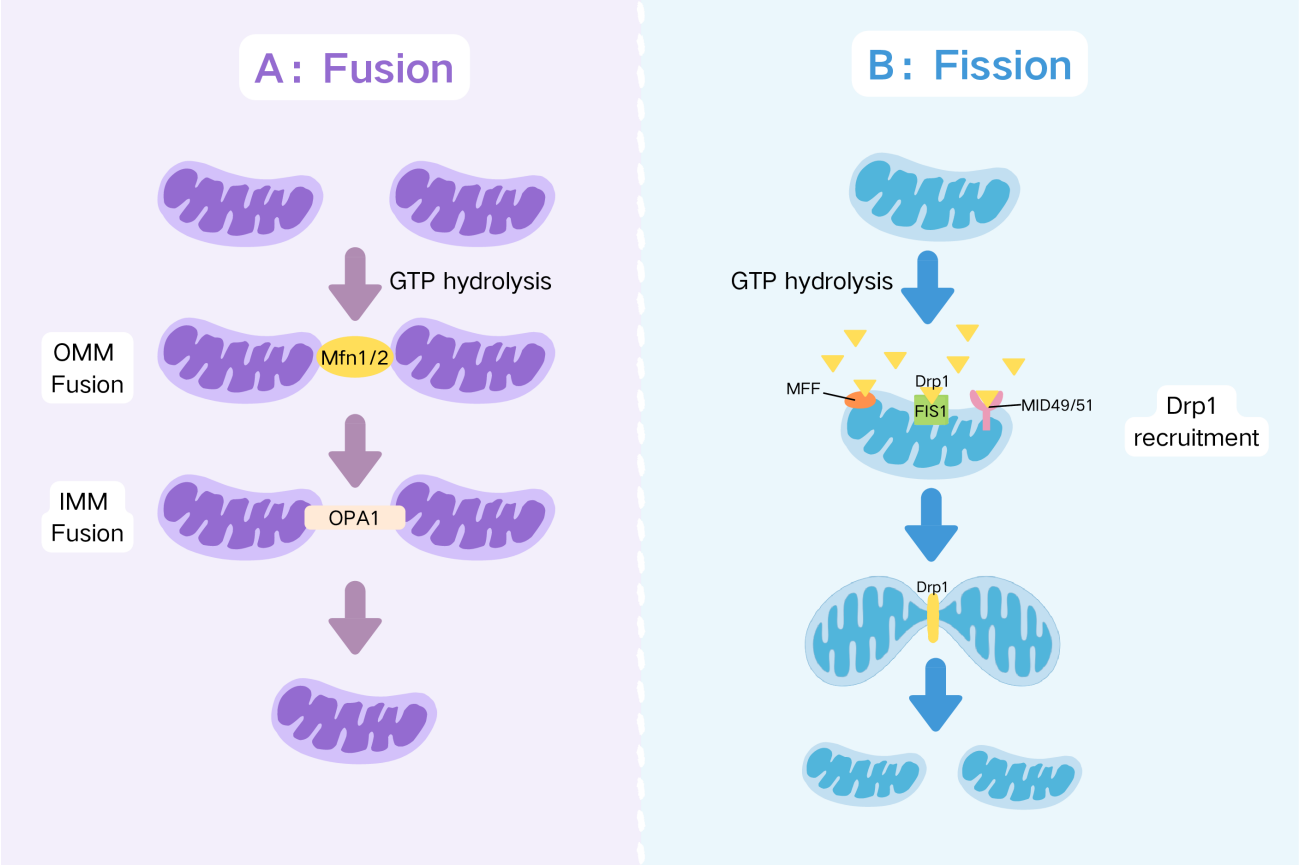

Fig. 3. The process of mitochondrial dynamics in mitochondrial quality control. (A) Under GTP hydrolysis, mitochondrial fusion occurs through the changes in the stereoconformation of MFN1/2 proteins on the two mitochondria and the docking of OPA1 proteins on the inner membrane, respectively resulting in OMM fusion and IMM fusion. (B) Mitochondrial fission is also a process in which proteins such as MID49, MID51, FIS1 and MFF on the mitochondrial membrane attract DRP1 in the cytoplasm under GTP hydrolysis and undergo spiral conformational changes. GTP, Guanosine triphosphate; MFN1/2, mitochondrial fusion protein 1/2; OPA1, optic atrophy 1; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; MID49/51, mitochondrial dynamics proteins of 49kDa/51kDa; MFF, mitochondrial fission factor; DRP1, dynamin-related protein 1.

role [153,154]. GTP hydrolysis drives helical contraction of DRP1 to complete mitochondrial scission [155]. Post-fission, the resulting daughter mitochondria often display unequal membrane potentials: the depolarized, damaged mitochondrion is targeted for mitophagy [156] (Fig. 3).

3.2.2.2 Pathological Targets. Therapeutic interventions targeting mitochondrial regulatory proteins have shown great clinical potential. Pharmacological regulation of key molecules, including DRP1, MFN2, and OPA1, can restore cellular homeostasis. Specific strategies focusing on post-translational modifications (PTMs) of MFN2 have been shown to be particularly effective in rebalancing mitochondrial dynamics [86,157]. DRP1 also initiates mitophagy via mitochondrial recruitment, a process linked to phosphorylation at Ser-616 and dephosphorylation at Ser-637, though the exact pathway remains unclear [158]. In MASH models with hepatic inflammation and fibrosis, overexpression of isocitrate dehydrogenase 2 (IDH2) reduces FIS1 and DRP1 levels [142]. Metformin activates AMPK signaling, promotes mitochondrial fission in high-fat diet (HFD)-fed mice, restores membrane potential, and upregulates ATP production [159]. In addition, it has been found that the natural compound naringenin can also regulate the AMPK pathway, increase mitochondrial fusion and reduce fission to activate apoptosis of cancer cells [160]. Resolvin D1 (RvD1) protects against hepatic ischemia-reperfusion injury by suppressing DRP1-mediated fission [161]. Mdivi-1, a DRP1 inhibitor, alleviates MASH by blocking pathological mitochondrial fragmentation [162,163]. Rhein similarly inhibits DRP1-dependent fission via the DRP1/PINK1/Parkin pathway, enhancing mitophagy and reducing apoptosis [164]. Pyridostigmine (PYR), an acetylcholinesterase inhibitor, improves mitochondrial morphology by upregulating ATP synthesis and OPA1, DRP1, and FIS1 expression [165]. Liraglutide stabilizes mitochondrial structure by increasing DRP1 and OPA1 levels [60].

3.3 Mitochondrial Biogenesis

3.3.1 Physiological Mechanism

Mitochondrial biogenesis refers to the process by which cells maintain energy metabolic homeostasis through the regulation of mitochondrial generation, proliferation, and functional remodeling. It coordinates mitochondrial and nuclear genomes, encompassing mtDNA transcription, translation, synthesis, import and assembly of nuclear DNA (nDNA)-encoded mitochondrial proteins, and other regulatory steps [166]. This process is primarily governed by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PGC-1*α) and its downstream signaling pathways [167]. As the central regulator of mitochondrial biogenesis, *PGC-1*α is activated by upstream Sirt1 and stimulates NRF1/NRF2 to promote mtDNA transcription, replication, and the expression of mitochondrial transcription factor A/B (*TFAM/TFBM*), ensuring mitochondrial genome stability [168,169]. *PGC-1*α also activates estrogen-related receptor alpha (ERRα) [170] and peroxisome proliferator-activated receptor alpha (PPARα) [171,172], upregulating SIRT3 to enhance mitochondrial protein synthesis. As a rule, during the MASH stage, bacterial signalling and inflammatory cytokines inhibit AMPK, thereby reducing mitochondrial biogenesis (Fig. 4).

3.3.2 Pathological Targets

Conditions like obesity, T2DM, cardiovascular disorders, and fatty liver are linked to compromised *PGC-1*α expression and its activity [173]. Dipicrylamine activates the AMPK-*PGC-1*α/ERRα pathway to elevate *SIRT3* levels, ameliorating mitochondrial dysfunction and oxidative stress [174]. Metformin upregulates *PGC-1*α expression in T2DM patients via AMPK activation, thereby restoring mitochondrial biogenesis [102]. Formoterol, a β2-adrenergic receptor agonist, induces mitochondrial biogenesis by phosphorylating Akt to produce NO, which activates soluble guanylate cyclase (sGC) [175]. Sofosbuvir (SOF), a nucleotide analog inhibitor of HCV polymerase, increases hepatic and muscular *PGC-1*α and NRF1 expression in young female rats [123]. Anthocyanins boost AMPK-*PGC-1*α signaling, thereby rejuvenating mitochondria, promoting their formation, and improving oxidative phosphorylation (OXPHOS) and fatty acid β-oxidation [176,177]. Moreover, Sitagliptin may dose-effectively increase *PGC-1*α and irisin levels, which could enhance insulin sensitivity, glucose and lipid metabolism, and mitigate inflammatory responses [178].

3.4 Mitochondrial Unfolded Protein Response

UPR^{mt} is a protective stress mechanism that restores cellular homeostasis by addressing misfolded or dysfunctional proteins within mitochondria [179]. Under mitochondrial proteostatic imbalance, mitochondrial matrix buildup of improperly folded proteins triggers UPR^{mt} signals. UPR^{mt} activation partially depends on FUNDC1-mediated mitophagy to reduce mtDNA stress [180] and involves mitochondrial ROS (mtROS) acting as signaling molecules to oxidize cytosolic chaperone DNAJA1 (HSP40) [181]. UPR^{mt} works primarily through two molecular pathways. The classical ATF4/ATF5-C/EBP-homologous protein (CHOP) cascade controls transcriptional stress adaptation, while the Sirt3-Forkhead box O3 (FOXO3a)-superoxide dismutase 2 (SOD2) axis coordinates redox homeostasis through enzymatic antioxidant regulation.

3.4.1 ATF4/ATF5-CHOP Pathway

3.4.1.1 Physiological Mechanism. In this pathway, *CHOP* transcription is induced by mitochondrial proteotoxic stress through the c-Jun N-terminal kinase (JNK) signaling cascade [182]. *CHOP*, part of the integrated stress response (ISR), upregulates mitochondrial chaperones (e.g., Hsp60, Hsp10, mtHsp70) and proteases (e.g., LONP1, ClpXP) to refold or degrade misfolded proteins [183,184,185,186]. Chaperones facilitate GTP-dependent protein folding and prevent cytoplasmic leakage of mitochondrial proteins [184], while proteases clear damaged proteins [185,186]. Although non-proteotoxic mitochondrial stress can induce CHOP via ATF4, this process lacks chaperone activation [183,187]. ATF5 translocates from mitochondria to the nucleus during stress, enhancing chaperone and protease transcription [188]. ISR activation phosphorylates eIF2α, promoting ATF4, ATF5, and CHOP activity [189] (Fig. 5).

3.4.1.2 Pathological Targets. PYR upregulates UPR^{mt} factors LONP1 and HSP60, alleviating obesity-induced liver injury [165]. Vacuolar H-ATPase (v-ATPase) activates mTORC1-dependent ATF4 phosphorylation to drive UPR^{mt} transcription [190]. Resveratrol modulates UPR^{mt} by upregulating *ATF4/ATF6* and downregulating *CHOP*, thereby mitigating ER stress [191]. Research indicates that nanoparticles infused with curcumin can jumpstart the autophagy process, thus safeguarding cells from dying off. This protective mechanism is believed to be tied to its ability to fine-tune the signaling pathway that's activated by eIF2α in the context of endoplasmic reticulum stress [192]. In addition, berberine may also primarily inhibit ER stress by targeting eIF2α [193].

3.4.2 Sirt3-FOXO3a-SOD2 Pathway

3.4.2.1 Physiological Mechanism. This pathway operates independently of ATF4/ATF5-*CHOP* and is activated by both proteotoxic stress and mitochondrial ROS [194]. During mitochondrial dysfunction, Sirt3 deacetylates *FOXO3a*, promoting its nuclear translocation and transcriptional activity. This enhances antioxidant enzymes SOD2 and catalase, reducing superoxide accumulation and oxidative damage [195,196]. Sirt3 also activates SOD2 via deacetylation, converting superoxide to hydrogen peroxide, which catalase further detoxifies to water [197]. This cascade mini-

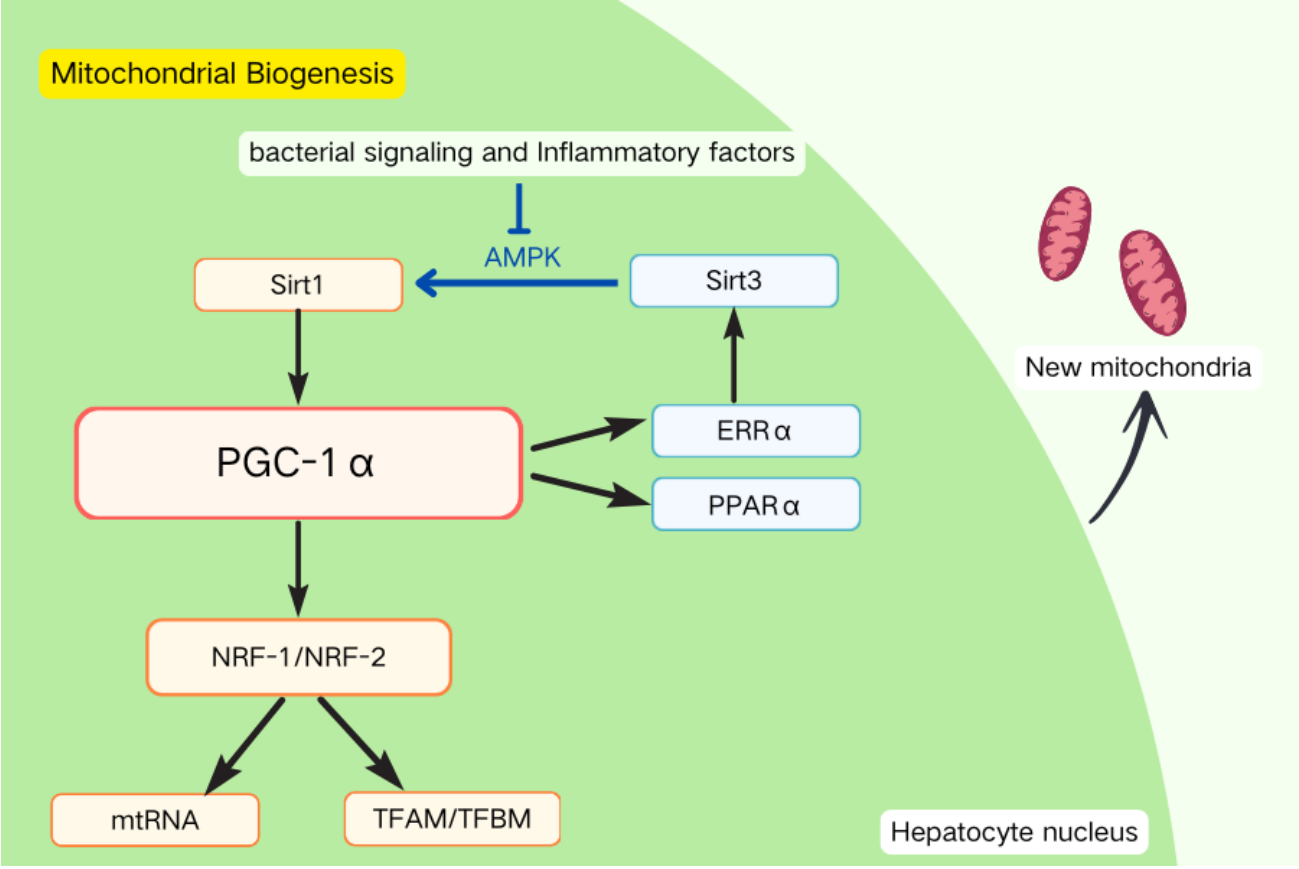

Fig. 4. The process of mitochondrial biogenesis in mitochondrial quality control. Mitochondrial biogenesis mainly involves the activation of *NRF-1/NRF-2* gene, AMPKα1/ULK1 pathway, and the binding of ERR and PPAR by *PGC-1*α protein, resulting in the transcription of mitochondrial RNA. AMPKα1, adenosine activated protein kinase α1; ULK1, Unc-51 like autophagy activating kinase 1; ERR, estrogen-related receptor; PPAR, peroxisome proliferators-activated receptors; *PGC-1*α, peroxisome proliferator-activated receptor gamma co-activator-1 alpha gene.

mizes oxidative protein misfolding in the matrix [198]. The pathway's interplay with PINK1-mediated mitophagy highlights novel mechanistic links between UPR^{mt} and MQC [199,200] (Fig. 5).

3.4.2.2 Pathological Targets. Liraglutide activates SIRT1/SIRT3-FOXO3a signaling, enhancing mitophagy and proteostasis to mitigate MASLD progression [60]. Hypoxia training reduces Sirt3, FOXO3a, and SOD2 levels in mice, suggesting Sirt3-FOXO3a signaling mediates hypoxia-induced mitophagy [201].

4. Drugs and Targets or Pathways

Clinically, many drugs have been shown to act on the corresponding targets and pathways of MQC, thereby achieving therapeutic effects for MASLD (Table 1, Ref. [17,60,100,102,103,113,114,120,122,123,143,144,145,159,160,161,162,163,164,165,174,175,176,177,178,190,191,192,193,202,203,204,205,206,207]).

5. Conclusion

This review systematically elucidates the critical role of MQC mechanisms, including mitophagy, mitochondrial dynamics, biogenesis, and UPR^{mt}, in the pathogenesis and progression of MASLD. Dysregulation of MQC disrupts mitochondrial homeostasis, driving fragmentation, metabolic impairment, and exacerbation of hepatic steatosis, inflammation, and cellular injury. Critically, defective mitophagy accelerates the accumulation of damaged mitochondria, amplifying oxidative stress and impairing hepatocyte regeneration. While pharmacological interventions targeting MQC components show therapeutic promise, significant mechanistic and translational limitations persist, necessitating critical appraisal:

(1) Interdependence of MQC Pathways: The complex temporal and mechanistic crosstalk between MQC pathways (e.g., mitochondrial fission enabling mitophagy vs. excessive fission disrupting network integrity) remains incompletely resolved. Emerging tools like CRISPR/Cas9-mediated gene editing offer unprecedented precision to dissect these interactions *in vivo* (e.g., conditional knockout of

Table 1. Drugs targeting MASLD.

Drugs	Subject of experimentation	Targets or pathways	References
Tryptanthrin	*in vitro* macrophages	NOD-like receptor thermal protein domain associated protein 3 (NLRP3)	[17]
Griseofulvin	*in vitro* cells and mice	nuclear factor kappa-B (NF-κB), cGAS-STING	[202]
Glycyrrhiza Uralensis Polysaccharides	mice	cGAS-STING	[203]
Licorice flavonoids	mice	cGAS-STING	[204]
Puerarin	mice	Nuclearfactor erythroidderived 2-like 2 (NRF2)/Glutathione peroxidase 4 (GPX4)	[205]
Auroursodeoxycholic acid	mice	Transferrin receptor protein (TFRC)	[206]
New sesquiterpenes and viridin derivatives	zebrafish	PTEN-induced putative kinase 1 (PINK1)/Parkin	[100]
Metformin	human	PINK1/Parkin, Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)	[102,159]
Atractyloside	mice	AMPK	[103]
Resveratrol/polydatin	*in vitro* hepatocytes	SIRT1, SIRT3, PINK1	[113,114]
Artesunate	*in vitro* hepatocytes	FUN14 domain containing 1 (FUNDC1)	[120]
Empagliflozin	mice	adenosine activated protein kinase α1 (AMPKα1), Unc-51 like autophagy activating kinase 1 (ULK1), FUNDC1	[122,207]
Liraglutide	mice	dynamin-related protein 1 (DRP1), optic atrophy 1 (OPA1)	[60]
Bitter gourd	mice	mitochondrial fusion protein 1/2 (MFN1/2)	[143]
Salvianolic acid B	mice	MFN1 /MFN2	[144]
Pioglitazone	mice	OPA1, MFN2, DRP1	[145]
Naringenin	*in vitro* cells and mice	AMPK	[160]
Resolvin D1	mice	DRP1	[161]
Mdivi-1	mice	DRP1	[162,163]
Rhein	mice	DRP1, PINK1/Parkin	[164]
Pyridostigmine (PYR)	mice	OPA1, DRP1, Fission 1 (FIS1)	[165]
Dihydromyricetin	*in vitro* hepatocytes and mice	AMPK-*PGC-1*α/estrogen-related receptor (ERRα)	[174]
Metformin	human	peroxisome proliferator-activated receptor gamma co-activator-1 alpha gene (*PGC-1*α)	[102]
Formoterol	New Zealand white rabbits	Akt-sGC	[175]
Sofosbuvir (SOF)	mice	*PGC-1*α, NRF1	[123]
Anthocyanin	mice	AMPK-PGC-1α	[176,177]
Sitagliptin	mice	*PGC-1*α	[178]
Pyridostigmine (PYR)	mice	LONP1, HSP60	[165]
v-ATP enzyme	mice	activating transcription factor 4/5 (ATF4/5)-C/EBP-homologous protein (CHOP)	[190]
Resveratrol	human	ATF4/6-CHOP	[191]
curcumin-loaded nanoparticles	*in vitro* cells	eIF2α	[192]
Berberine	mice	eIF2α	[193]
Liraglutide	mice	Sirt3-Forkhead box O3 (FOXO3a)-superoxide dismutase 2 (SOD2)	[60]

PINK1, Parkin, or fission/fusion regulators), enabling targeted validation of therapeutic nodes.

(2) Pharmacological Limitations and Clinical Translation: Current MQC-targeting drugs (e.g., fission inhibitors, mitophagy inducers) face substantial hurdles: poor tissue specificity, off-target effects, and inadequate pharmacokinetics for sustained hepatic exposure. Many compounds lack isoform selectivity, raising safety concerns. Moreover, efficacy data remain largely confined to rodent models or *in vitro* systems, with minimal human validation. Human clinical trials are urgently needed but are hampered by the absence of reliable biomarkers to stratify patients based on MQC dysfunction phenotypes and monitor target engagement. Critically, most agents target single MQC nodes, failing to address the interconnected nature of MQC failure in MASLD. This "whack-a-mole" approach risks therapeutic dead ends without combinatorial strategies.

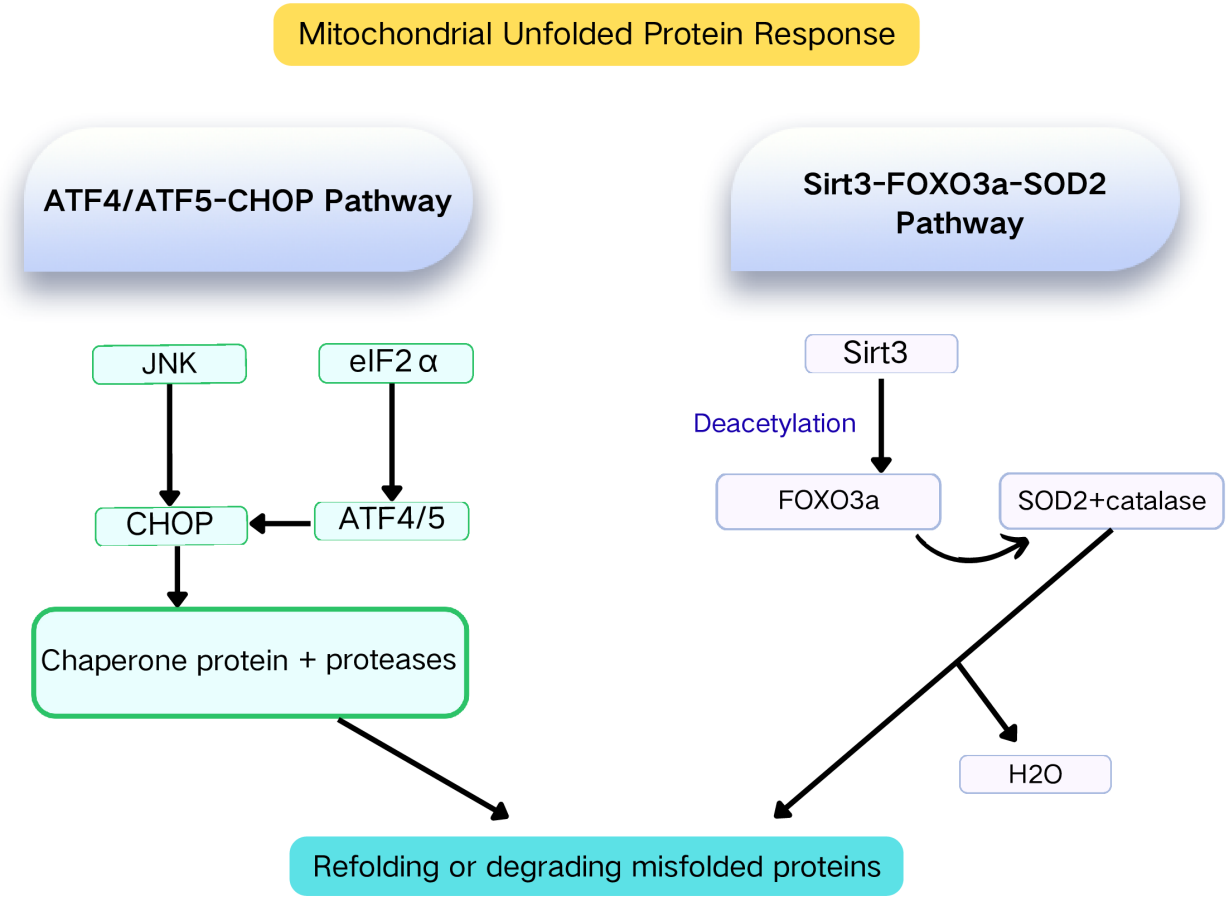

Fig. 5. The process of mitochondrial unfolded protein response (UPR^{mt}) in mitochondrial quality control. UPR^{mt} is mainly performed through the ATF4/ATF5-CHOP and Sirt3-FOXO3a-SOD2 pathways, but other pathways may also exist. ATF4/ATF5-CHOP pathway can eventually form chaperone proteins and proteases to clear damaged or misfolded proteins. Sirt3-FOXO3a-SOD2 pathway can ultimately reduce the accumulation of mitochondrial superoxide, which is also closely related to the PINK1 pathway to a certain extent. ATF, activating transcription factor; CHOP, C/EBP-homologous protein; FOXO3a, Forkhead box O3; SOD2, superoxide dismutase 2.

(3) Impaired Liver Regeneration: MQC dysfunction critically undermines hepatocyte regeneration in advanced MASLD, particularly post-resection. Downregulation of β-oxidation regulators (PPARα, CPT1α) and disrupted signaling (e.g., PPARβ/Akt/E2F) impair energy supply and proliferation [208,209]. Direct mechanistic links between MQC failure and regeneration defects warrant urgent investigation using lineage-tracing models and human explants.

Furthermore, while MQC modulation holds compelling mechanistic promise for MASLD, its clinical viability hinges on resolving pharmacological shortcomings, advancing human studies, and integrating systemic therapies. CRISPR-driven target discovery and MQC-specific biomarker development represent critical frontiers for de-risking translation and personalizing interventions.

Author Contributions

XC and MM designed the research study. ZJG and SBO developed the overall concept. YG and HZ integrated and refined the key highlights. WKF and JQW planned out each chapter, created the first and full version of the article. NL conducted the literature search. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by The Innovation Key Project of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (No. 2022s470).

Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used Deepseek-R1 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

References

[1] Sanyal AJ, Friedman SL, McCullough AJ, Dimick-Santos L. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American Association for the Study of Liver Diseases-U.S. Food and Drug Administration Joint Workshop. Hepatology. 2015; 61: 1392–1405. https://doi.org/10.1002/hep.27678.

[2] Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. Journal of Hepatology. 2024; 80: e76–e77. https://doi.org/10.1016/j.jhep.2023.08.026.

[3] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016; 64: 73–84. https://doi.org/10.1002/hep.28431.

[4] Gadiparthi C, Spatz M, Greenberg S, Iqbal U, Kanna S, Satapathy SK, et al. NAFLD Epidemiology, Emerging Pharmacotherapy, Liver Transplantation Implications and the Trends in the United States. Journal of Clinical and Translational Hepatology. 2020; 8: 215–221. https://doi.org/10.14218/JCTH.2020.00014.

[5] Zhou XD, Targher G, Byrne CD, Somers V, Kim SU, Chahal CAA, et al. An international multidisciplinary consensus statement on MAFLD and the risk of CVD. Hepatology International. 2023; 17: 773–791. https://doi.org/10.1007/s12072-023-10543-8.

[6] Kaya E, Yilmaz Y. Metabolic-associated Fatty Liver Disease (MAFLD): A Multi-systemic Disease Beyond the Liver. Journal of Clinical and Translational Hepatology. 2022; 10: 329–338. https://doi.org/10.14218/JCTH.2021.00178.

[7] Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023; 77: 1335–1347. https://doi.org/10.1097/HEP.0000000000000004.

[8] Chang X, Lochner A, Wang HH, Wang S, Zhu H, Ren J, et al. Coronary microvascular injury in myocardial infarction: perception and knowledge for mitochondrial quality control. Theranostics. 2021; 11: 6766–6785. https://doi.org/10.7150/thno.60143.

[9] Zhao S, Guo Y, Yin X. Autophagy, Ferroptosis, Apoptosis and Pyroptosis in Metabolic Dysfunction-Associated Steatotic Liver Disease. Front Biosci (Landmark Ed). 2024; 29: 30. https://doi.org/10.31083/j.fbl2901030.

[10] Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism: Clinical and Experimental. 2016; 65: 1038–1048. https://doi.org/10.1016/j.metabol.2015.12.012.

[11] Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell. 2021; 184: 2537–2564. https://doi.org/10.1016/j.cell.2021.04.015.

[12] Xu X, Poulsen KL, Wu L, Liu S, Miyata T, Song Q, et al. Targeted therapeutics and novel signaling pathways in non-alcohol-associated fatty liver/steatohepatitis (NAFL/NASH). Signal Transduction and Targeted Therapy. 2022; 7: 287. https://doi.org/10.1038/s41392-022-01119-3.

[13] Deprince A, Haas JT, Staels B. Dysregulated lipid metabolism links NAFLD to cardiovascular disease. Molecular Metabolism. 2020; 42: 101092. https://doi.org/10.1016/j.molmet.2020.101092.

[14] Haemmerle G, Lass A, Zimmermann R, Gorkiewicz G, Meyer C, Rozman J, et al. Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. Science. 2006; 312: 734–737. https://doi.org/10.1126/science.1123965.

[15] Szabo G, Iracheta-Vellve A. Inflammasome activation in the liver: Focus on alcoholic and non-alcoholic steatohepatitis. Clinics and Research in Hepatology and Gastroenterology. 2015; 39: S18–S23. https://doi.org/10.1016/j.clinre.2015.06.012.

[16] Koyama Y, Brenner DA. Liver inflammation and fibrosis. The Journal of Clinical Investigation. 2017; 127: 55–64. https://doi.org/10.1172/JCI88881.

[17] Ren L, Yang H, Wang H, Qin S, Zhan X, Li H, et al. Tryptanthrin suppresses multiple inflammasome activation to regulate NASH progression by targeting ASC protein. Phytomedicine. 2024; 131: 155758. https://doi.org/10.1016/j.phymed.2024.155758.

[18] Bourebaba N, Marycz K. Hepatic stellate cells role in the course of metabolic disorders development - A molecular overview. Pharmacological Research. 2021; 170: 105739. https://doi.org/10.1016/j.phrs.2021.105739.

[19] Zhang B, Roh YS, Liang S, Liu C, Naiki M, Masuda K, et al. Neurotropin suppresses inflammatory cytokine expression and cell death through suppression of NF-κB and JNK in hepatocytes. PLoS ONE. 2014; 9: e114071. https://doi.org/10.1371/journal.pone.0114071.

[20] Mirea AM, Tack CJ, Chavakis T, Joosten LAB, Toonen EJM. IL-1 Family Cytokine Pathways Underlying NAFLD: Towards New Treatment Strategies. Trends in Molecular Medicine. 2018; 24: 458–471. https://doi.org/10.1016/j.molmed.2018.03.005.

[21] Wenfeng Z, Yakun W, Di M, Jianping G, Chuanxin W, Chun H. Kupffer cells: increasingly significant role in nonalcoholic fatty liver disease. Annals of Hepatology. 2014; 13: 489–495.

[22] Guilliams M, Scott CL. Liver macrophages in health and disease. Immunity. 2022; 55: 1515–1529. https://doi.org/10.1016/j.immuni.2022.08.002.

[23] Luo X, Li H, Ma L, Zhou J, Guo X, Woo SL, et al. Expression of STING Is Increased in Liver Tissues From Patients With NAFLD and Promotes Macrophage-Mediated Hepatic Inflammation and Fibrosis in Mice. Gastroenterology. 2018; 155: 1971–1984.e4. https://doi.org/10.1053/j.gastro.2018.09.010.

[24] Kim JY, Yang IS, Kim HJ, Yoon JY, Han YH, Seong JK, et al. RORα contributes to the maintenance of genome ploidy in the liver of mice with diet-induced nonalcoholic steatohepatitis. American Journal of Physiology. Endocrinology and Metabolism. 2022; 322: E118–E131. https://doi.org/10.1152/ajpendo.00309.2021.

[25] Safari Z, Gérard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Cellular and Molecular Life Sciences. 2019; 76: 1541–1558. https://doi.org/10.1007/s00018-019-03011-w.

[26] Khanmohammadi S, Kuchay MS. Toll-like receptors and metabolic (dysfunction)-associated fatty liver disease. Pharmacological Research. 2022; 185: 106507. https://doi.org/10.1016/j.phrs.2022.106507.

[27] Mouries J, Brescia P, Silvestri A, Spadoni I, Sorribas M, Wiest R, et al. Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. Journal of Hepatology. 2019; 71: 1216–1228. https://doi.org/

10.1016/j.jhep.2019.08.005.
[28] Chen Y, Xie C, Lei Y, Ye D, Wang L, Xiong F, et al. Theabrownin from Qingzhuan tea prevents high-fat diet-induced MASLD via regulating intestinal microbiota. Biomedicine & Pharmacotherapy. 2024; 174: 116582. https://doi.org/10.1016/j.biopha.2024.116582.
[29] Lin X, Zou X, Hu B, Sheng D, Zhu T, Yin M, et al. Bi Xie Fen Qing Yin decoction alleviates potassium oxonate and adenine induced-hyperuricemic nephropathy in mice by modulating gut microbiota and intestinal metabolites. Biomedicine & Pharmacotherapy. 2024; 170: 116022. https://doi.org/10.1016/j.biopha.2023.116022.
[30] Krengel U, Törnroth-Horsefield S. Biochemistry. Coping with oxidative stress. Science. 2015; 347: 125–126. https://doi.org/10.1126/science.aaa3602.
[31] Masarone M, Rosato V, Dallio M, Gravina AG, Aglitti A, Loguercio C, et al. Role of Oxidative Stress in Pathophysiology of Nonalcoholic Fatty Liver Disease. Oxidative Medicine and Cellular Longevity. 2018; 2018: 9547613. https://doi.org/10.1155/2018/9547613.
[32] Mikhed Y, Daiber A, Steven S. Mitochondrial Oxidative Stress, Mitochondrial DNA Damage and Their Role in Age-Related Vascular Dysfunction. International Journal of Molecular Sciences. 2015; 16: 15918–15953. https://doi.org/10.3390/ijms160715918.
[33] Yang S, Lian G. ROS and diseases: role in metabolism and energy supply. Molecular and Cellular Biochemistry. 2020; 467: 1–12. https://doi.org/10.1007/s11010-019-03667-9.
[34] Xu J, Peng Y, Zeng Y, Hua YQ, Xu XL. 2, 3, 4', 5-tetrahydroxystilbene-2-0-β-d Glycoside Attenuates Age- and Diet-Associated Non-Alcoholic Steatohepatitis and Atherosclerosis in LDL Receptor Knockout Mice and Its Possible Mechanisms. International Journal of Molecular Sciences. 2019; 20: 1617. https://doi.org/10.3390/ijms20071617.
[35] Knebel B, Fahlbusch P, Dille M, Wahlers N, Hartwig S, Jacob S, et al. Fatty Liver Due to Increased *de novo* Lipogenesis: Alterations in the Hepatic Peroxisomal Proteome. Frontiers in Cell and Developmental Biology. 2019; 7: 248. https://doi.org/10.3389/fcell.2019.00248.
[36] Chen Z, Tian R, She Z, Cai J, Li H. Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. Free Radical Biology & Medicine. 2020; 152: 116–141. https://doi.org/10.1016/j.freeradbiomed.2020.02.025.
[37] Begriche K, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. Mitochondrion. 2006; 6: 1–28. https://doi.org/10.1016/j.mito.2005.10.004.
[38] Farzanegi P, Dana A, Ebrahimpoor Z, Asadi M, Azarbayjani MA. Mechanisms of beneficial effects of exercise training on non-alcoholic fatty liver disease (NAFLD): Roles of oxidative stress and inflammation. European Journal of Sport Science. 2019; 19: 994–1003. https://doi.org/10.1080/17461391.2019.1571114.
[39] Zhao RZ, Jiang S, Zhang L, Yu ZB. Mitochondrial electron transport chain, ROS generation and uncoupling (Review). International Journal of Molecular Medicine. 2019; 44: 3–15. https://doi.org/10.3892/ijmm.2019.4188.
[40] Deshwal S, Antonucci S, Kaludercic N, Di Lisa F. Measurement of Mitochondrial ROS Formation. Methods in Molecular Biology. 2018; 1782: 403–418. https://doi.org/10.1007/978-1-4939-7831-1_24.
[41] Ji L, Fu F, Zhang L, Liu W, Cai X, Zhang L, et al. Insulin attenuates myocardial ischemia/reperfusion injury via reducing oxidative/nitrative stress. American Journal of Physiology. Endocrinology and Metabolism. 2010; 298: E871–E880. https://doi.org/10.1152/ajpendo.00623.2009.
[42] Chowdhury A, Santra A, Bhattacharjee K, Ghatak S, Saha DR, Dhali GK. Mitochondrial oxidative stress and permeability transition in isoniazid and rifampicin induced liver injury in mice. Journal of Hepatology. 2006; 45: 117–126. https://doi.org/10.1016/j.jhep.2006.01.027.
[43] Nakanishi T, Kawasaki Y, Nakamura Y, Kimura Y, Kawamura K, Shumba MN, et al. An implication of the mitochondrial carrier SLC25A3 as an oxidative stress modulator in NAFLD. Experimental Cell Research. 2023; 431: 113740. https://doi.org/10.1016/j.yexcr.2023.113740.
[44] Jeong HS, Kim KH, Lee IS, Park JY, Kim Y, Kim KS, et al. Ginkgolide A ameliorates non-alcoholic fatty liver diseases on high fat diet mice. Biomedicine & Pharmacotherapy. 2017; 88: 625–634. https://doi.org/10.1016/j.biopha.2017.01.114.
[45] Fromenty B, Robin MA, Igoudjil A, Mansouri A, Pessayre D. The ins and outs of mitochondrial dysfunction in NASH. Diabetes & Metabolism. 2004; 30: 121–138. https://doi.org/10.1016/s1262-3636(07)70098-8.
[46] Serviddio G, Sastre J, Bellanti F, Viña J, Vendemiale G, Altomare E. Mitochondrial involvement in non-alcoholic steatohepatitis. Molecular Aspects of Medicine. 2008; 29: 22–35. https://doi.org/10.1016/j.mam.2007.09.014.
[47] Moro T, Nakao S, Sumiyoshi H, Ishii T, Miyazawa M, Ishii N, et al. A Combination of Mitochondrial Oxidative Stress and Excess Fat/Calorie Intake Accelerates Steatohepatitis by Enhancing Hepatic CC Chemokine Production in Mice. PLoS ONE. 2016; 11: e0146592. https://doi.org/10.1371/journal.pone.0146592.
[48] Meakin PJ, Chowdhry S, Sharma RS, Ashford FB, Walsh SV, McCrimmon RJ, et al. Susceptibility of Nrf2-null mice to steatohepatitis and cirrhosis upon consumption of a high-fat diet is associated with oxidative stress, perturbation of the unfolded protein response, and disturbance in the expression of metabolic enzymes but not with insulin resistance. Molecular and Cellular Biology. 2014; 34: 3305–3320. https://doi.org/10.1128/MCB.00677-14.
[49] Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, et al. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biology. 2019; 20: 247–260. https://doi.org/10.1016/j.redox.2018.09.025.
[50] Strzyz P. AMPK against NASH. Nature Reviews. Molecular Cell Biology. 2020; 21: 181. https://doi.org/10.1038/s41580-020-0225-0.
[51] Solano-Urrusquieta A, Morales-González JA, Castro-Narro GE, Cerda-Reyes E, Flores-Rangel PD, Fierros-Oceguera R. NRF-2 and nonalcoholic fatty liver disease. Annals of Hepatology. 2020; 19: 458–465. https://doi.org/10.1016/j.aohep.2019.11.010.
[52] Mao H, Chen W, Chen L, Li L. Potential role of mitochondria-associated endoplasmic reticulum membrane proteins in diseases. Biochemical Pharmacology. 2022; 199: 115011. https://doi.org/10.1016/j.bcp.2022.115011.
[53] Chyau CC, Wang HF, Zhang WJ, Chen CC, Huang SH, Chang CC, et al. Antrodan Alleviates High-Fat and High-Fructose Diet-Induced Fatty Liver Disease in C57BL/6 Mice Model via AMPK/Sirt1/SREBP-1c/PPARγ Pathway. International Journal of Molecular Sciences. 2020; 21: 360. https://doi.org/10.3390/ijms21010360.
[54] Sun L, Wang X, Saredy J, Yuan Z, Yang X, Wang H. Innate-adaptive immunity interplay and redox regulation in immune response. Redox Biology. 2020; 37: 101759. https://doi.org/10.1016/j.redox.2020.101759.
[55] Westerouen Van Meeteren MJ, Drenth JPH, Tjwa ETTL. Elafibranor: a potential drug for the treatment of nonalcoholic steatohepatitis (NASH). Expert Opinion on Investigational Drugs. 2020; 29: 117–123. https://doi.org/10.1080/13543784.2020.1668375.

[56] Li W, Cao T, Luo C, Cai J, Zhou X, Xiao X, et al. Crosstalk between ER stress, NLRP3 inflammasome, and inflammation. Applied Microbiology and Biotechnology. 2020; 104: 6129–6140. https://doi.org/10.1007/s00253-020-10614-y.

[57] Shao G, Liu Y, Lu L, Zhang G, Zhou W, Wu T, et al. The Pathogenesis of HCC Driven by NASH and the Preventive and Therapeutic Effects of Natural Products. Frontiers in Pharmacology. 2022; 13: 944088. https://doi.org/10.3389/fphar.2022.944088.

[58] Nasiri-Ansari N, Nikolopoulou C, Papoutsi K, Kyrou I, Mantzoros CS, Kyriakopoulos G, et al. Empagliflozin Attenuates Non-Alcoholic Fatty Liver Disease (NAFLD) in High Fat Diet Fed ApoE$^{(-/-)}$ Mice by Activating Autophagy and Reducing ER Stress and Apoptosis. International Journal of Molecular Sciences. 2021; 22: 818. https://doi.org/10.3390/ijms22020818.

[59] Liu C, Zhou B, Meng M, Zhao W, Wang D, Yuan Y, et al. FOXA3 induction under endoplasmic reticulum stress contributes to non-alcoholic fatty liver disease. Journal of Hepatology. 2021; 75: 150–162. https://doi.org/10.1016/j.jhep.2021.01.042.

[60] Tong W, Ju L, Qiu M, Xie Q, Chen Y, Shen W, et al. Liraglutide ameliorates non-alcoholic fatty liver disease by enhancing mitochondrial architecture and promoting autophagy through the SIRT1/SIRT3-FOXO3a pathway. Hepatology Research. 2016; 46: 933–943. https://doi.org/10.1111/hepr.12634.

[61] Chang X, Liu R, Li R, Peng Y, Zhu P, Zhou H. Molecular Mechanisms of Mitochondrial Quality Control in Ischemic Cardiomyopathy. International Journal of Biological Sciences. 2023; 19: 426–448. https://doi.org/10.7150/ijbs.76223.

[62] Jamwal S, Blackburn JK, Elsworth JD. PPARγ/PGC1α signaling as a potential therapeutic target for mitochondrial biogenesis in neurodegenerative disorders. Pharmacology & Therapeutics. 2021; 219: 107705. https://doi.org/10.1016/j.pharmthera.2020.107705.

[63] Brumatti G, Salmanidis M, Ekert PG. Crossing paths: interactions between the cell death machinery and growth factor survival signals. Cellular and Molecular Life Sciences. 2010; 67: 1619–1630. https://doi.org/10.1007/s00018-010-0288-8.

[64] Bedoui S, Herold MJ, Strasser A. Emerging connectivity of programmed cell death pathways and its physiological implications. Nature Reviews. Molecular Cell Biology. 2020; 21: 678–695. https://doi.org/10.1038/s41580-020-0270-8.

[65] Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. Cell Research. 2019; 29: 347–364. https://doi.org/10.1038/s41422-019-0164-5.

[66] Quarato G, Mari L, Barrows NJ, Yang M, Ruehl S, Chen MJ, et al. Mitophagy restricts BAX/BAK-independent, Parkin-mediated apoptosis. Science Advances. 2023; 9: eadg8156. https://doi.org/10.1126/sciadv.adg8156.

[67] Zeng C, Duan F, Hu J, Luo B, Huang B, Lou X, et al. NLRP3 inflammasome-mediated pyroptosis contributes to the pathogenesis of non-ischemic dilated cardiomyopathy. Redox Biology. 2020; 34: 101523. https://doi.org/10.1016/j.redox.2020.101523.

[68] Wang Y, Xiong L, Yao Y, Ma Y, Liu Q, Pang Y, et al. The involvement of DRP1-mediated caspase-1 activation in inflammatory response by urban particulate matter in EA.hy926 human vascular endothelial cells. Environmental Pollution. 2021; 287: 117369. https://doi.org/10.1016/j.envpol.2021.117369.

[69] Liu Z, Wang M, Wang X, Bu Q, Wang Q, Su W, et al. XBP1 deficiency promotes hepatocyte pyroptosis by impairing mitophagy to activate mtDNA-cGAS-STING signaling in macrophages during acute liver injury. Redox Biology. 2022; 52: 102305. https://doi.org/10.1016/j.redox.2022.102305.

[70] Yuk JM, Silwal P, Jo EK. Inflammasome and Mitophagy Connection in Health and Disease. International Journal of Molecular Sciences. 2020; 21: 4714. https://doi.org/10.3390/ijms21134714.

[71] Sabouny R, Fraunberger E, Geoffrion M, Ng ACH, Baird SD, Screaton RA, et al. The Keap1-Nrf2 Stress Response Pathway Promotes Mitochondrial Hyperfusion Through Degradation of the Mitochondrial Fission Protein Drp1. Antioxidants & Redox Signaling. 2017; 27: 1447–1459. https://doi.org/10.1089/ars.2016.6855.

[72] Su LJ, Zhang JH, Gomez H, Murugan R, Hong X, Xu D, et al. Reactive Oxygen Species-Induced Lipid Peroxidation in Apoptosis, Autophagy, and Ferroptosis. Oxidative Medicine and Cellular Longevity. 2019; 2019: 5080843. https://doi.org/10.1155/2019/5080843.

[73] Lin Q, Li S, Jin H, Cai H, Zhu X, Yang Y, et al. Mitophagy alleviates cisplatin-induced renal tubular epithelial cell ferroptosis through ROS/HO-1/GPX4 axis. International Journal of Biological Sciences. 2023; 19: 1192–1210. https://doi.org/10.7150/ijbs.80775.

[74] Monzel AS, Enríquez JA, Picard M. Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction. Nature Metabolism. 2023; 5: 546–562. https://doi.org/10.1038/s42255-023-00783-1.

[75] Roca-Portoles A, Tait SWG. Mitochondrial quality control: from molecule to organelle. Cellular and Molecular Life Sciences. 2021; 78: 3853–3866. https://doi.org/10.1007/s00018-021-03775-0.

[76] Chang X, Li Y, Liu J, Wang Y, Guan X, Wu Q, et al. ß-tubulin contributes to Tongyang Huoxue decoction-induced protection against hypoxia/reoxygenation-induced injury of sinoatrial node cells through SIRT1-mediated regulation of mitochondrial quality surveillance. Phytomedicine. 2023; 108: 154502. https://doi.org/10.1016/j.phymed.2022.154502.

[77] Picca A, Faitg J, Auwerx J, Ferrucci L, D'Amico D. Mitophagy in human health, ageing and disease. Nature Metabolism. 2023; 5: 2047–2061. https://doi.org/10.1038/s42255-023-00930-8.

[78] Mishra E, Thakur MK. Mitophagy: A promising therapeutic target for neuroprotection during ageing and age-related diseases. British Journal of Pharmacology. 2023; 180: 1542–1561. https://doi.org/10.1111/bph.16062.

[79] Gustafsson ÅB, Dorn GW, 2nd. Evolving and Expanding the Roles of Mitophagy as a Homeostatic and Pathogenic Process. Physiological Reviews. 2019; 99: 853–892. https://doi.org/10.1152/physrev.00005.2018.

[80] Chen G, Kroemer G, Kepp O. Mitophagy: An Emerging Role in Aging and Age-Associated Diseases. Frontiers in Cell and Developmental Biology. 2020; 8: 200. https://doi.org/10.3389/fcell.2020.00200.

[81] Valente EM, Abou-Sleiman PM, Caputo V, Muqit MMK, Harvey K, Gispert S, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science. 2004; 304: 1158–1160. https://doi.org/10.1126/science.1096284.

[82] Narendra D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. The Journal of Cell Biology. 2008; 183: 795–803. https://doi.org/10.1083/jcb.200809125.

[83] Okatsu K, Uno M, Koyano F, Go E, Kimura M, Oka T, et al. A dimeric PINK1-containing complex on depolarized mitochondria stimulates Parkin recruitment. The Journal of Biological Chemistry. 2013; 288: 36372–36384. https://doi.org/10.1074/jbc.M113.509653.

[84] Rasool S, Soya N, Truong L, Croteau N, Lukacs GL, Trempe JF. PINK1 autophosphorylation is required for ubiquitin recognition. EMBO Reports. 2018; 19: e44981. https://doi.org/10.15252/embr.201744981.

[85] Li J, Dang X, Franco A, Dorn GW, 2nd. Reciprocal Regulation of Mitofusin 2-Mediated Mitophagy and Mitochondrial Fusion by Different PINK1 Phosphorylation Events. Frontiers in Cell

and Developmental Biology. 2022; 10: 868465. https://doi.org/10.3389/fcell.2022.868465.
[86] Bayne AN, Trempe JF. Mechanisms of PINK1, ubiquitin and Parkin interactions in mitochondrial quality control and beyond. Cellular and Molecular Life Sciences. 2019; 76: 4589–4611. https://doi.org/10.1007/s00018-019-03203-4.
[87] Bernardini JP, Lazarou M, Dewson G. Parkin and mitophagy in cancer. Oncogene. 2017; 36: 1315–1327. https://doi.org/10.1038/onc.2016.302.
[88] Kawajiri S, Saiki S, Sato S, Sato F, Hatano T, Eguchi H, et al. PINK1 is recruited to mitochondria with parkin and associates with LC3 in mitophagy. FEBS Letters. 2010; 584: 1073–1079. https://doi.org/10.1016/j.febslet.2010.02.016.
[89] Sekine S, Youle RJ. PINK1 import regulation; a fine system to convey mitochondrial stress to the cytosol. BMC Biology. 2018; 16: 2. https://doi.org/10.1186/s12915-017-0470-7.
[90] Durcan TM, Tang MY, Pérusse JR, Dashti EA, Aguileta MA, McLelland GL, et al. USP8 regulates mitophagy by removing K6-linked ubiquitin conjugates from parkin. The EMBO Journal. 2014; 33: 2473–2491. https://doi.org/10.15252/embj.201489729.
[91] Bingol B, Tea JS, Phu L, Reichelt M, Bakalarski CE, Song Q, et al. The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature. 2014; 510: 370–375. https://doi.org/10.1038/nature13418.
[92] Onishi M, Yamano K, Sato M, Matsuda N, Okamoto K. Molecular mechanisms and physiological functions of mitophagy. The EMBO Journal. 2021; 40: e104705. https://doi.org/10.15252/embj.2020104705.
[93] Kirkin V, Lamark T, Johansen T, Dikic I. NBR1 cooperates with p62 in selective autophagy of ubiquitinated targets. Autophagy. 2009; 5: 732–733. https://doi.org/10.4161/auto.5.5.8566.
[94] Wong YC, Holzbaur ELF. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111: E4439–E4448. https://doi.org/10.1073/pnas.1405752111.
[95] Richter B, Sliter DA, Herhaus L, Stolz A, Wang C, Beli P, et al. Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria. Proceedings of the National Academy of Sciences of the United States of America. 2016; 113: 4039–4044. https://doi.org/10.1073/pnas.1523926113.
[96] Jin K, Shi Y, Zhang H, Zhangyuan G, Wang F, Li S, et al. A TNFα/Miz1-positive feedback loop inhibits mitophagy in hepatocytes and propagates non-alcoholic steatohepatitis. Journal of Hepatology. 2023; 79: 403–416. https://doi.org/10.1016/j.jhep.2023.03.039.
[97] Kondapalli C, Kazlauskaite A, Zhang N, Woodroof HI, Campbell DG, Gourlay R, et al. PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating Serine 65. Open Biology. 2012; 2: 120080. https://doi.org/10.1098/rsob.120080.
[98] Wauer T, Swatek KN, Wagstaff JL, Gladkova C, Pruneda JN, Michel MA, et al. Ubiquitin Ser65 phosphorylation affects ubiquitin structure, chain assembly and hydrolysis. The EMBO Journal. 2015; 34: 307–325. https://doi.org/10.15252/embj.201489847.
[99] Wang L, Cho YL, Tang Y, Wang J, Park JE, Wu Y, et al. PTEN-L is a novel protein phosphatase for ubiquitin dephosphorylation to inhibit PINK1-Parkin-mediated mitophagy. Cell Research. 2018; 28: 787–802. https://doi.org/10.1038/s41422-018-0056-0.
[100] Zhang H, You Y, Xu J, Jiang H, Jiang J, Su Z, et al. New sesquiterpenes and viridin derivatives from Penicillium sp. Ameliorates NAFLD by regulating the PINK1/Parkin mitophagy pathway. Bioorganic Chemistry. 2024; 151: 107656. https://doi.org/10.1016/j.bioorg.2024.107656.
[101] Gonçalves IO, Passos E, Diogo CV, Rocha-Rodrigues S, Santos-Alves E, Oliveira PJ, et al. Exercise mitigates mitochondrial permeability transition pore and quality control mechanisms alterations in nonalcoholic steatohepatitis. Applied Physiology, Nutrition, and Metabolism. 2016; 41: 298–306. https://doi.org/10.1139/apnm-2015-0470.
[102] de Marañón AM, Díaz-Pozo P, Canet F, Díaz-Morales N, Abad-Jiménez Z, López-Domènech S, et al. Metformin modulates mitochondrial function and mitophagy in peripheral blood mononuclear cells from type 2 diabetic patients. Redox Biology. 2022; 53: 102342. https://doi.org/10.1016/j.redox.2022.102342.
[103] Zhang P, Cheng X, Sun H, Li Y, Mei W, Zeng C. Atractyloside Protect Mice Against Liver Steatosis by Activation of Autophagy *via* ANT-AMPK-mTORC1 Signaling Pathway. Frontiers in Pharmacology. 2021; 12: 736655. https://doi.org/10.3389/fphar.2021.736655.
[104] Xu HD, Qin ZH. Beclin 1, Bcl-2 and Autophagy. Advances in Experimental Medicine and Biology. 2019; 1206: 109–126. https://doi.org/10.1007/978-981-15-0602-4_5.
[105] Mazure NM, Pouysségur J. Atypical BH3-domains of BNIP3 and BNIP3L lead to autophagy in hypoxia. Autophagy. 2009; 5: 868–869. https://doi.org/10.4161/auto.9042.
[106] Schwarten M, Mohrlüder J, Ma P, Stoldt M, Thielmann Y, Stangler T, et al. Nix directly binds to GABARAP: a possible crosstalk between apoptosis and autophagy. Autophagy. 2009; 5: 690–698. https://doi.org/10.4161/auto.5.5.8494.
[107] Palikaras K, Lionaki E, Tavernarakis N. Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. Nature Cell Biology. 2018; 20: 1013–1022. https://doi.org/10.1038/s41556-018-0176-2.
[108] Li Y, Zheng W, Lu Y, Zheng Y, Pan L, Wu X, et al. BNIP3L/NIX-mediated mitophagy: molecular mechanisms and implications for human disease. Cell Death & Disease. 2021; 13: 14. https://doi.org/10.1038/s41419-021-04469-y.
[109] Wilhelm LP, Zapata-Muñoz J, Villarejo-Zori B, Pellegrin S, Freire CM, Toye AM, et al. BNIP3L/NIX regulates both mitophagy and pexophagy. The EMBO Journal. 2022; 41: e111115. https://doi.org/10.15252/embj.2022111115.
[110] Yamashita SI, Sugiura Y, Matsuoka Y, Maeda R, Inoue K, Furukawa K, et al. Mitophagy mediated by BNIP3 and NIX protects against ferroptosis by downregulating mitochondrial reactive oxygen species. Cell Death and Differentiation. 2024; 31: 651–661. https://doi.org/10.1038/s41418-024-01280-y.
[111] Zeng C, Chen M. Progress in Nonalcoholic Fatty Liver Disease: SIRT Family Regulates Mitochondrial Biogenesis. Biomolecules. 2022; 12: 1079. https://doi.org/10.3390/biom12081079.
[112] Tian C, Huang R, Xiang M. SIRT1: Harnessing multiple pathways to hinder NAFLD. Pharmacological Research. 2024; 203: 107155. https://doi.org/10.1016/j.phrs.2024.107155.
[113] Zhang Y, Chen ML, Zhou Y, Yi L, Gao YX, Ran L, et al. Resveratrol improves hepatic steatosis by inducing autophagy through the cAMP signaling pathway. Molecular Nutrition & Food Research. 2015; 59: 1443–1457. https://doi.org/10.1002/mnfr.201500016.
[114] He J, Qian YC, Yin YC, Kang JR, Pan TR. Polydatin: a potential NAFLD therapeutic drug that regulates mitochondrial autophagy through SIRT3-FOXO3-BNIP3 and PINK1-PRKN mechanisms - a network pharmacology and experimental investigation. Chemico-Biological Interactions. 2024; 398: 111110. https://doi.org/10.1016/j.cbi.2024.111110.
[115] Li K, Xia X, Tong Y. Multiple roles of mitochondrial au-

tophagy receptor FUNDC1 in mitochondrial events and kidney disease. Frontiers in Cell and Developmental Biology. 2024; 12: 1453365. https://doi.org/10.3389/fcell.2024.1453365.
[116] Chen M, Chen Z, Wang Y, Tan Z, Zhu C, Li Y, et al. Mitophagy receptor FUNDC1 regulates mitochondrial dynamics and mitophagy. Autophagy. 2016; 12: 689–702. https://doi.org/10.1080/15548627.2016.1151580.
[117] van Vliet AR, Chiduza GN, Maslen SL, Pye VE, Joshi D, De Tito S, et al. ATG9A and ATG2A form a heteromeric complex essential for autophagosome formation. Molecular Cell. 2022; 82: 4324–4339.e8. https://doi.org/10.1016/j.molcel.2022.10.017.
[118] Bi Y, Liu S, Qin X, Abudureyimu M, Wang L, Zou R, et al. FUNDC1 interacts with GPx4 to govern hepatic ferroptosis and fibrotic injury through a mitophagy-dependent manner. Journal of Advanced Research. 2024; 55: 45–60. https://doi.org/10.1016/j.jare.2023.02.012.
[119] Li W, Zhang X, Zhuang H, Chen HG, Chen Y, Tian W, et al. MicroRNA-137 is a novel hypoxia-responsive microRNA that inhibits mitophagy via regulation of two mitophagy receptors FUNDC1 and NIX. The Journal of Biological Chemistry. 2014; 289: 10691–10701. https://doi.org/10.1074/jbc.M113.537050.
[120] Ma Z, Chen W, Liu Y, Yu L, Mao X, Guo X, et al. Artesunate Sensitizes human hepatocellular carcinoma to sorafenib via exacerbating AFAP1L2-SRC-FUNDC1 axis-dependent mitophagy. Autophagy. 2024; 20: 541–556. https://doi.org/10.1080/15548627.2023.2261758.
[121] Sun J, Chen C, Wang J. Artesunate Inhibits Lipid Accumulation and Inflammation by Regulating the NLRP3 Inflammasome in Nonalcoholic Fatty Liver Disease. Discovery Medicine. 2024; 36: 385–392. https://doi.org/10.24976/Discov.Med.202436181.36.
[122] Yu W, Wang L, Ren WY, Xu HX, Wu NN, Yu DH, et al. SGLT2 inhibitor empagliflozin alleviates cardiac remodeling and contractile anomalies in a FUNDC1-dependent manner in experimental Parkinson's disease. Acta Pharmacologica Sinica. 2024; 45: 87–97. https://doi.org/10.1038/s41401-023-01144-0.
[123] Hafez HA, Atoom AM, Khafaga RHM, Shaker SA, Kamel MA, Assem NM, et al. Direct-Acting Antiviral Drug Modulates the Mitochondrial Biogenesis in Different Tissues of Young Female Rats. International Journal of Molecular Sciences. 2023; 24: 15844. https://doi.org/10.3390/ijms242115844.
[124] Panconesi R, Widmer J, Carvalho MF, Eden J, Dondossola D, Dutkowski P, et al. Mitochondria and ischemia reperfusion injury. Current Opinion in Organ Transplantation. 2022; 27: 434–445. https://doi.org/10.1097/MOT.0000000000001015.
[125] Jang S, Javadov S. OPA1 regulates respiratory supercomplexes assembly: The role of mitochondrial swelling. Mitochondrion. 2020; 51: 30–39. https://doi.org/10.1016/j.mito.2019.11.006.
[126] Adebayo M, Singh S, Singh AP, Dasgupta S. Mitochondrial fusion and fission: The fine-tune balance for cellular homeostasis. FASEB Journal. 2021; 35: e21620. https://doi.org/10.1096/fj.202100067R.
[127] Koshiba T, Detmer SA, Kaiser JT, Chen H, McCaffery JM, Chan DC. Structural basis of mitochondrial tethering by mitofusin complexes. Science. 2004; 305: 858–862. https://doi.org/10.1126/science.1099793.
[128] Zhang M, Bener MB, Jiang Z, Wang T, Esencan E, Scott Iii R, et al. Mitofusin 1 is required for female fertility and to maintain ovarian follicular reserve. Cell Death & Disease. 2019; 10: 560. https://doi.org/10.1038/s41419-019-1799-3.
[129] Hu L, Ding M, Tang D, Gao E, Li C, Wang K, et al. Targeting mitochondrial dynamics by regulating Mfn2 for therapeutic intervention in diabetic cardiomyopathy. Theranostics. 2019; 9: 3687–3706. https://doi.org/10.7150/thno.33684.
[130] Yan L, Qi Y, Huang X, Yu C, Lan L, Guo X, et al. Structural basis for GTP hydrolysis and conformational change of MFN1 in mediating membrane fusion. Nature Structural & Molecular Biology. 2018; 25: 233–243. https://doi.org/10.1038/s41594-018-0034-8.
[131] Cao YL, Meng S, Chen Y, Feng JX, Gu DD, Yu B, et al. MFN1 structures reveal nucleotide-triggered dimerization critical for mitochondrial fusion. Nature. 2017; 542: 372–376. https://doi.org/10.1038/nature21077.
[132] Li YJ, Cao YL, Feng JX, Qi Y, Meng S, Yang JF, et al. Structural insights of human mitofusin-2 into mitochondrial fusion and CMT2A onset. Nature Communications. 2019; 10: 4914. https://doi.org/10.1038/s41467-019-12912-0.
[133] Gao S, Hu J. Mitochondrial Fusion: The Machineries In and Out. Trends in Cell Biology. 2021; 31: 62–74. https://doi.org/10.1016/j.tcb.2020.09.008.
[134] Franco A, Kitsis RN, Fleischer JA, Gavathiotis E, Kornfeld OS, Gong G, et al. Correcting mitochondrial fusion by manipulating mitofusin conformations. Nature. 2016; 540: 74–79. https://doi.org/10.1038/nature20156.
[135] Li P, Wang J, Zhao X, Ru J, Tian T, An Y, et al. PTEN inhibition attenuates endothelial cell apoptosis in coronary heart disease via modulating the AMPK-CREB-Mfn2-mitophagy signaling pathway. Journal of Cellular Physiology. 2020; 235: 4878–4889. https://doi.org/10.1002/jcp.29366.
[136] Bian X, Klemm RW, Liu TY, Zhang M, Sun S, Sui X, et al. Structures of the atlastin GTPase provide insight into homotypic fusion of endoplasmic reticulum membranes. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 3976–3981. https://doi.org/10.1073/pnas.1101643108.
[137] Byrnes LJ, Sondermann H. Structural basis for the nucleotide-dependent dimerization of the large G protein atlastin-1/SPG3A. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 2216–2221. https://doi.org/10.1073/pnas.1012792108.
[138] Zhang D, Zhang Y, Ma J, Zhu C, Niu T, Chen W, et al. Cryo-EM structures of S-OPA1 reveal its interactions with membrane and changes upon nucleotide binding. eLife. 2020; 9: e50294. https://doi.org/10.7554/eLife.50294.
[139] Yu C, Zhao J, Yan L, Qi Y, Guo X, Lou Z, et al. Structural insights into G domain dimerization and pathogenic mutation of OPA1. The Journal of Cell Biology. 2020; 219: e201907098. https://doi.org/10.1083/jcb.201907098.
[140] Meeusen S, DeVay R, Block J, Cassidy-Stone A, Wayson S, McCaffery JM, et al. Mitochondrial inner-membrane fusion and crista maintenance requires the dynamin-related GTPase Mgm1. Cell. 2006; 127: 383–395. https://doi.org/10.1016/j.cell.2006.09.021.
[141] Twig G, Shirihai OS. The interplay between mitochondrial dynamics and mitophagy. Antioxidants & Redox Signaling. 2011; 14: 1939–1951. https://doi.org/10.1089/ars.2010.3779.
[142] Gong F, Gao L, Ding T. IDH2 protects against nonalcoholic steatohepatitis by alleviating dyslipidemia regulated by oxidative stress. Biochemical and Biophysical Research Communications. 2019; 514: 593–600. https://doi.org/10.1016/j.bbrc.2019.04.069.
[143] Xu J, Cao K, Li Y, Zou X, Chen C, Szeto IMY, et al. Bitter gourd inhibits the development of obesity-associated fatty liver in C57BL/6 mice fed a high-fat diet. The Journal of Nutrition. 2014; 144: 475–483. https://doi.org/10.3945/jn.113.187450.
[144] Wang YC, Kong WZ, Jin QM, Chen J, Dong L. Effects of salvianolic acid B on liver mitochondria of rats with nonalcoholic steatohepatitis. World Journal of Gastroenterology. 2015; 21: 10104–10112. https://doi.org/10.3748/wjg.v21.i35.10104.
[145] Sun L, Yuan Q, Xu T, Yao L, Feng J, Ma J, et al. Pioglitazone Improves Mitochondrial Function in the Remnant Kid-

ney and Protects against Renal Fibrosis in 5/6 Nephrectomized Rats. Frontiers in Pharmacology. 2017; 8: 545. https://doi.org/10.3389/fphar.2017.00545.

[146] Sumneang N, Siri-Angkul N, Kumfu S, Chattipakorn SC, Chattipakorn N. The effects of iron overload on mitochondrial function, mitochondrial dynamics, and ferroptosis in cardiomyocytes. Archives of Biochemistry and Biophysics. 2020; 680: 108241. https://doi.org/10.1016/j.abb.2019.108241.

[147] Kleinbongard P, Skyschally A, Gent S, Pesch M, Heusch G. STAT3 as a common signal of ischemic conditioning: a lesson on "rigor and reproducibility" in preclinical studies on cardioprotection. Basic Research in Cardiology. 2017; 113: 3. https://doi.org/10.1007/s00395-017-0660-z.

[148] Smirnova E, Griparic L, Shurland DL, van der Bliek AM. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Molecular Biology of the Cell. 2001; 12: 2245–2256. https://doi.org/10.1091/mbc.12.8.2245.

[149] Zerihun M, Sukumaran S, Qvit N. The Drp1-Mediated Mitochondrial Fission Protein Interactome as an Emerging Core Player in Mitochondrial Dynamics and Cardiovascular Disease Therapy. International Journal of Molecular Sciences. 2023; 24: 5785. https://doi.org/10.3390/ijms24065785.

[150] Ong SB, Hausenloy DJ. Mitochondrial Dynamics as a Therapeutic Target for Treating Cardiac Diseases. Handbook of Experimental Pharmacology. 2017; 240: 251–279. https://doi.org/10.1007/164_2016_7.

[151] Osellame LD, Singh AP, Stroud DA, Palmer CS, Stojanovski D, Ramachandran R, et al. Cooperative and independent roles of the Drp1 adaptors Mff, MiD49 and MiD51 in mitochondrial fission. Journal of Cell Science. 2016; 129: 2170–2181. https://doi.org/10.1242/jcs.185165.

[152] Otera H, Miyata N, Kuge O, Mihara K. Drp1-dependent mitochondrial fission via MiD49/51 is essential for apoptotic cristae remodeling. The Journal of Cell Biology. 2016; 212: 531–544. https://doi.org/10.1083/jcb.201508099.

[153] Losón OC, Song Z, Chen H, Chan DC. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Molecular Biology of the Cell. 2013; 24: 659–667. https://doi.org/10.1091/mbc.E12-10-0721.

[154] Kraus F, Ryan MT. The constriction and scission machineries involved in mitochondrial fission. Journal of Cell Science. 2017; 130: 2953–2960. https://doi.org/10.1242/jcs.199562.

[155] Kalia R, Wang RYR, Yusuf A, Thomas PV, Agard DA, Shaw JM, et al. Structural basis of mitochondrial receptor binding and constriction by DRP1. Nature. 2018; 558: 401–405. https://doi.org/10.1038/s41586-018-0211-2.

[156] Breitzig MT, Alleyn MD, Lockey RF, Kolliputi N. A mitochondrial delicacy: dynamin-related protein 1 and mitochondrial dynamics. American Journal of Physiology. Cell Physiology. 2018; 315: C80–C90. https://doi.org/10.1152/ajpcell.00042.2018.

[157] Ordureau A, Paulo JA, Zhang J, An H, Swatek KN, Cannon JR, et al. Global Landscape and Dynamics of Parkin and USP30-Dependent Ubiquitylomes in iNeurons during Mitophagic Signaling. Molecular Cell. 2020; 77: 1124–1142.e10. https://doi.org/10.1016/j.molcel.2019.11.013.

[158] Tong M, Zablocki D, Sadoshima J. The role of Drp1 in mitophagy and cell death in the heart. Journal of Molecular and Cellular Cardiology. 2020; 142: 138–145. https://doi.org/10.1016/j.yjmcc.2020.04.015.

[159] Wang Y, An H, Liu T, Qin C, Sesaki H, Guo S, et al. Metformin Improves Mitochondrial Respiratory Activity through Activation of AMPK. Cell Reports. 2019; 29: 1511–1523.e5. https://doi.org/10.1016/j.celrep.2019.09.070.

[160] Wang D, Zhou Y, Hua L, Hu M, Zhu N, Liu Y, et al. The role of the natural compound naringenin in AMPK-mitochondria modulation and colorectal cancer inhibition. Phytomedicine. 2024; 131: 155786. https://doi.org/10.1016/j.phymed.2024.155786.

[161] Kang JW, Choi HS, Lee SM. Resolvin D1 attenuates liver ischaemia/reperfusion injury through modulating thioredoxin 2-mediated mitochondrial quality control. British Journal of Pharmacology. 2018; 175: 2441–2453. https://doi.org/10.1111/bph.14212.

[162] Ding J, Zhang Z, Li S, Wang W, Du T, Fang Q, et al. Mdivi-1 alleviates cardiac fibrosis post myocardial infarction at infarcted border zone, possibly via inhibition of Drp1-Activated mitochondrial fission and oxidative stress. Archives of Biochemistry and Biophysics. 2022; 718: 109147. https://doi.org/10.1016/j.abb.2022.109147.

[163] Elbadawy M, Tanabe K, Yamamoto H, Ishihara Y, Mochizuki M, Abugomaa A, et al. Evaluation of the efficacy of mitochondrial fission inhibitor (Mdivi-1) using non-alcoholic steatohepatitis (NASH) liver organoids. Frontiers in Pharmacology. 2023; 14: 1243258. https://doi.org/10.3389/fphar.2023.1243258.

[164] Li H, Jia Y, Yao D, Gao M, Wang L, Liu J. Rhein alleviates myocardial ischemic injury by inhibiting mitochondrial division, activating mitochondrial autophagy and suppressing myocardial cell apoptosis through the Drp1/Pink1/Parkin pathway. Molecular Biology Reports. 2024; 51: 266. https://doi.org/10.1007/s11033-023-09154-1.

[165] Xue R, Wu Q, Guo L, Ye D, Cao Q, Zhang M, et al. Pyridostigmine attenuated high-fat-diet induced liver injury by the reduction of mitochondrial damage and oxidative stress via α7nAChR and M3AChR. Journal of Biochemical and Molecular Toxicology. 2024; 38: e23671. https://doi.org/10.1002/jbt.23671.

[166] Popov LD. Mitochondrial biogenesis: An update. Journal of Cellular and Molecular Medicine. 2020; 24: 4892–4899. https://doi.org/10.1111/jcmm.15194.

[167] Lehman JJ, Barger PM, Kovacs A, Saffitz JE, Medeiros DM, Kelly DP. Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. The Journal of Clinical Investigation. 2000; 106: 847–856. https://doi.org/10.1172/JCI10268.

[168] Ngo HB, Lovely GA, Phillips R, Chan DC. Distinct structural features of TFAM drive mitochondrial DNA packaging versus transcriptional activation. Nature Communications. 2014; 5: 3077. https://doi.org/10.1038/ncomms4077.

[169] Tran MT, Zsengeller ZK, Berg AH, Khankin EV, Bhasin MK, Kim W, et al. PGC1α drives NAD biosynthesis linking oxidative metabolism to renal protection. Nature. 2016; 531: 528–532. https://doi.org/10.1038/nature17184.

[170] Fan S, Yan X, Hu X, Liu X, Zhao S, Zhang Y, et al. Shikonin blocks CAF-induced TNBC metastasis by suppressing mitochondrial biogenesis through GSK-3β/NEDD4-1 mediated phosphorylation-dependent degradation of PGC-1α. Journal of Experimental & Clinical Cancer Research. 2024; 43: 180. https://doi.org/10.1186/s13046-024-03101-z.

[171] Li DD, Ma JM, Li MJ, Gao LL, Fan YN, Zhang YN, et al. Supplementation of *Lycium barbarum* Polysaccharide Combined with Aerobic Exercise Ameliorates High-Fat-Induced Nonalcoholic Steatohepatitis via AMPK/PPARα/PGC-1α Pathway. Nutrients. 2022; 14: 3247. https://doi.org/10.3390/nu14153247.

[172] Liao J, Xie X, Wang N, Wang Y, Zhao J, Chen F, et al. Formononetin promotes fatty acid β-oxidation to treat non-alcoholic steatohepatitis through SIRT1/PGC-1α/PPARα pathway. Phytomedicine. 2024; 124: 155285. https://doi.org/10.1016/j.phymed.2023.155285.

[173] Wu H, Deng X, Shi Y, Su Y, Wei J, Duan H. PGC-1α, glucose metabolism and type 2 diabetes mellitus. The Journal of Endocrinology. 2016; 229: R99–R115. https://doi.org/10.1530/JOE-16-0021.

[174] Zeng X, Yang J, Hu O, Huang J, Ran L, Chen M, et al. Di-

hydromyricetin Ameliorates Nonalcoholic Fatty Liver Disease by Improving Mitochondrial Respiratory Capacity and Redox Homeostasis Through Modulation of SIRT3 Signaling. Antioxidants & Redox Signaling. 2019; 30: 163–183. https://doi.org/10.1089/ars.2017.7172.

[175] Cameron RB, Peterson YK, Beeson CC, Schnellmann RG. Author Correction: Structural and pharmacological basis for the induction of mitochondrial biogenesis by formoterol but not clenbuterol. Scientific Reports. 2019; 9: 6790. https://doi.org/10.1038/s41598-019-42463-9.

[176] Ling W, Shen T, Tang X, Jiang X. Anthocyanins Improved Mitochondrial Dysfunction in Mice of Non-alcoholic Fatty Liver Disease Induced by High Fat Diet. The FASEB Journal. 2016; 30: 915–929. https://doi.org/10.1096/fasebj.30.1_supplement.915.29.

[177] Tang X, Shen T, Jiang X, Xia M, Sun X, Guo H, et al. Purified anthocyanins from bilberry and black currant attenuate hepatic mitochondrial dysfunction and steatohepatitis in mice with methionine and choline deficiency. Journal of Agricultural and Food Chemistry. 2015; 63: 552–561. https://doi.org/10.1021/jf504926n.

[178] Liu Y, Xu F, Jiang P. Effect of sitagliptin on expression of skeletal muscle peroxisome proliferator-activated receptor γ coactivator-1α and irisin in a rat model of type 2 diabetes mellitus. The Journal of International Medical Research. 2020; 48: 300060519885569. https://doi.org/10.1177/0300060519885569.

[179] Zhao Q, Wang J, Levichkin IV, Stasinopoulos S, Ryan MT, Hoogenraad NJ. A mitochondrial specific stress response in mammalian cells. The EMBO Journal. 2002; 21: 4411–4419. https://doi.org/10.1093/emboj/cdf445.

[180] Ji H, Wang J, Muid D, Song W, Jiang Y, Zhou H. FUNDC1 activates the mitochondrial unfolded protein response to preserve mitochondrial quality control in cardiac ischemia/reperfusion injury. Cellular Signalling. 2022; 92: 110249. https://doi.org/10.1016/j.cellsig.2022.110249.

[181] Sutandy FXR, Gößner I, Tascher G, Münch C. A cytosolic surveillance mechanism activates the mitochondrial UPR. Nature. 2023; 618: 849–854. https://doi.org/10.1038/s41586-023-06142-0.

[182] Jaeschke A, Karasarides M, Ventura JJ, Ehrhardt A, Zhang C, Flavell RA, et al. JNK2 is a positive regulator of the cJun transcription factor. Molecular Cell. 2006; 23: 899–911. https://doi.org/10.1016/j.molcel.2006.07.028.

[183] Münch C, Harper JW. Mitochondrial unfolded protein response controls matrix pre-RNA processing and translation. Nature. 2016; 534: 710–713. https://doi.org/10.1038/nature18302.

[184] Okamoto T, Yamamoto H, Kudo I, Matsumoto K, Odaka M, Grave E, et al. HSP60 possesses a GTPase activity and mediates protein folding with HSP10. Scientific Reports. 2017; 7: 16931. https://doi.org/10.1038/s41598-017-17167-7.

[185] Pareek G, Pallanck LJ. Inactivation of Lon protease reveals a link between mitochondrial unfolded protein stress and mitochondrial translation inhibition. Cell Death & Disease. 2018; 9: 1168. https://doi.org/10.1038/s41419-018-1213-6.

[186] Al-Furoukh N, Ianni A, Nolte H, Hölper S, Krüger M, Wanrooij S, et al. ClpX stimulates the mitochondrial unfolded protein response (UPRmt) in mammalian cells. Biochimica et Biophysica Acta. 2015; 1853: 2580–2591. https://doi.org/10.1016/j.bbamcr.2015.06.016.

[187] Quirós PM, Prado MA, Zamboni N, D'Amico D, Williams RW, Finley D, et al. Multi-omics analysis identifies ATF4 as a key regulator of the mitochondrial stress response in mammals. The Journal of Cell Biology. 2017; 216: 2027–2045. https://doi.org/10.1083/jcb.201702058.

[188] Fiorese CJ, Schulz AM, Lin YF, Rosin N, Pellegrino MW, Haynes CM. The Transcription Factor ATF5 Mediates a Mammalian Mitochondrial UPR. Current Biology. 2016; 26: 2037–2043. https://doi.org/10.1016/j.cub.2016.06.002.

[189] Naresh NU, Haynes CM. Signaling and Regulation of the Mitochondrial Unfolded Protein Response. Cold Spring Harbor Perspectives in Biology. 2019; 11: a033944. https://doi.org/10.1101/cshperspect.a033944.

[190] Li TY, Wang Q, Gao AW, Li X, Sun Y, Mottis A, et al. Lysosomes mediate the mitochondrial UPR via mTORC1-dependent ATF4 phosphorylation. Cell Discovery. 2023; 9: 92. https://doi.org/10.1038/s41421-023-00589-1.

[191] Brenjian S, Moini A, Yamini N, Kashani L, Faridmojtahedi M, Bahramrezaie M, et al. Resveratrol treatment in patients with polycystic ovary syndrome decreased pro-inflammatory and endoplasmic reticulum stress markers. American Journal of Reproductive Immunology. 2020; 83: e13186. https://doi.org/10.1111/aji.13186.

[192] Gu Y, Xia H, Chen X, Li J. Curcumin Nanoparticles Attenuate Lipotoxic Injury in Cardiomyocytes Through Autophagy and Endoplasmic Reticulum Stress Signaling Pathways. Frontiers in Pharmacology. 2021; 12: 571482. https://doi.org/10.3389/fphar.2021.571482.

[193] Wu Y, Chen Q, Wen B, Wu N, He B, Chen J. Berberine Reduces Aβ_42 Deposition and Tau Hyperphosphorylation *via* Ameliorating Endoplasmic Reticulum Stress. Frontiers in Pharmacology. 2021; 12: 640758. https://doi.org/10.3389/fphar.2021.640758.

[194] Zhou Z, Fan Y, Zong R, Tan K. The mitochondrial unfolded protein response: A multitasking giant in the fight against human diseases. Ageing Research Reviews. 2022; 81: 101702. https://doi.org/10.1016/j.arr.2022.101702.

[195] Papa L, Germain D. Correction for Papa and Germain, "SirT3 Regulates a Novel Arm of the Mitochondrial Unfolded Protein Response". Molecular and Cellular Biology. 2017; 37: e00191-17. https://doi.org/10.1128/MCB.00191-17.

[196] Tao R, Vassilopoulos A, Parisiadou L, Yan Y, Gius D. Regulation of MnSOD enzymatic activity by Sirt3 connects the mitochondrial acetylome signaling networks to aging and carcinogenesis. Antioxidants & Redox Signaling. 2014; 20: 1646–1654. https://doi.org/10.1089/ars.2013.5482.

[197] Wang S, Zhang J, Deng X, Zhao Y, Xu K. Advances in characterization of SIRT3 deacetylation targets in mitochondrial function. Biochimie. 2020; 179: 1–13. https://doi.org/10.1016/j.biochi.2020.08.021.

[198] Newman JC, He W, Verdin E. Mitochondrial protein acylation and intermediary metabolism: regulation by sirtuins and implications for metabolic disease. The Journal of Biological Chemistry. 2012; 287: 42436–42443. https://doi.org/10.1074/jbc.R112.404863.

[199] Yang J, Yu Z, Jiang Y, Zhang Z, Tian Y, Cai J, et al. SIRT3 alleviates painful diabetic neuropathy by mediating the FoxO3a-PINK1-Parkin signaling pathway to activate mitophagy. CNS Neuroscience & Therapeutics. 2024; 30: e14703. https://doi.org/10.1111/cns.14703.

[200] Huang L, Yao T, Chen J, Zhang Z, Yang W, Gao X, et al. Effect of Sirt3 on retinal pigment epithelial cells in high glucose through Foxo3a/ PINK1-Parkin pathway mediated mitophagy. Experimental Eye Research. 2022; 218: 109015. https://doi.org/10.1016/j.exer.2022.109015.

[201] Ma C, Zhao Y, Ding X, Gao B. The role of Sirt3 in the changes of skeletal muscle mitophagy induced by hypoxic training. General Physiology and Biophysics. 2022; 41: 447–455. https://doi.org/10.4149/gpb_2022023.

[202] Yu N, Fu Y, Fan Q, Lin L, Ning Z, Leng D, et al. Antitumor properties of griseofulvin and its toxicity. Frontiers in Pharmacology. 2024; 15: 1459539. https://doi.org/10.3389/fphar.2024.

1459539.

[203] Hui S, Kan W, Qin S, He P, Zhao J, Li H, et al. *Glycyrrhiza uralensis* polysaccharides ameliorates cecal ligation and puncture-induced sepsis by inhibiting the cGAS-STING signaling pathway. Frontiers in Pharmacology. 2024; 15: 1374179. https://doi.org/10.3389/fphar.2024.1374179.

[204] Wen J, Qin S, Li Y, Zhang P, Zhan X, Fang M, et al. Flavonoids derived from licorice suppress LPS-induced acute lung injury in mice by inhibiting the cGAS-STING signaling pathway. Food and Chemical Toxicology. 2023; 175: 113732. https://doi.org/10.1016/j.fct.2023.113732.

[205] Dai C, Zhen F, Yu L, Xin S. Puerarin alleviates oxaliplatin-induced neuropathic pain by promoting Nrf2/GPX4-mediated antioxidative response. PLoS ONE. 2024; 19: e0308872. https://doi.org/10.1371/journal.pone.0308872.

[206] Li FJ, Abudureyimu M, Zhang ZH, Tao J, Ceylan AF, Lin J, et al. Inhibition of ER stress using tauroursodeoxycholic acid rescues obesity-evoked cardiac remodeling and contractile anomalies through regulation of ferroptosis. Chemico-Biological Interactions. 2024; 398: 111104. https://doi.org/10.1016/j.cbi.2024.111104.

[207] Cai C, Guo Z, Chang X, Li Z, Wu F, He J, et al. Corrigendum to "Empagliflozin attenuates cardiac microvascular ischemia/reperfusion through activating the AMPKα1/ULK1/FUNDC1/mitophagy pathway" [Redox Biol. 52 (2022) 102288]. Redox Biology. 2023; 63: 102738. https://doi.org/10.1016/j.redox.2023.102738.

[208] Qu X, Wen Y, Jiao J, Zhao J, Sun X, Wang F, et al. PARK7 deficiency inhibits fatty acid β-oxidation via PTEN to delay liver regeneration after hepatectomy. Clinical and Translational Medicine. 2022; 12: e1061. https://doi.org/10.1002/ctm2.1061.

[209] Liu HX, Fang Y, Hu Y, Gonzalez FJ, Fang J, Wan YJY. PPARβ Regulates Liver Regeneration by Modulating Akt and E2f Signaling. PLoS ONE. 2013; 8: e65644. https://doi.org/10.1371/journal.pone.0065644.