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REVIEW

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Mitochondrial quality control in alcohol-associated liver disease

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Abstract

Excessive alcohol consumption is a leading cause of alcohol-associated liver disease (ALD), a significant global health concern with limited therapeutic options. Understanding the key factors contributing to ALD pathogenesis is crucial for identifying potential therapeutic targets. Central to ALD pathogenesis is the intricate interplay between alcohol metabolism and cellular processes, particularly involving mitochondria. Mitochondria are essential organelles in the liver, critical for energy production and metabolic functions. However, they are particularly vulnerable to alcohol-induced damage due to their involvement in alcohol metabolism. Alcohol disrupts mitochondrial function, impairing ATP production and triggering oxidative stress, which leads to cellular damage and inflammation. Mitochondrial quality control mechanisms, including biogenesis, dynamics, and mitophagy, are crucial for maintaining optimal mitochondrial function. Chronic alcohol consumption disrupts mitochondrial quality control checkpoints, leading to mitochondrial dysfunction that impairs fatty acid oxidation and contributes to hepatic steatosis in ALD. Moreover, alcohol promotes the accumulation of damaged mitochondria and the release of proinflammatory components, exacerbating

Abbreviations: ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; ADH, alcohol dehydrogenase; AH, alcoholic hepatitis; ALD, alcohol-associated liver disease; ALDH2, acetaldehyde dehydrogenase 2; AMPK, AMP-activated protein kinase; ATF4, activating transcription factor 4; BAK, Bcl-2 homologous antagonist/killer; BAP31, B-cell receptor associated protein 31; BAX, BCL-2 associated X; cGamp, 2′3′-cyclic GMP-AMP; cGas, cyclic guanosine monophosphate-adenosine monophosphate (AMP) synthase; CK2, casein kinase 2; CPT1, carnitine palmitoyl transferase 1; CRT, calreticulin; Cx32, connexin 32; CypD, cyclophilin D; Cyp2E1, cytochrome P450 family 2 subfamily E member 1; DNA-Pkcs, DNA-dependent protein kinase catalytic subunit; DRP1, dynamin-related protein 1; Eif2α, eukaryotic translation initiation factor 2 subunit A; ER, endoplasmic reticulum; Erp57, ER protein 57; ETC, electron transport chain; FIS1, mitochondrial fission 1; FUNDC1, FUN14 domain-containing 1; GFP, green fluorescent protein; GRP75, glucose-regulated protein 75; IFN, interferon; IMM, inner mitochondria membrane; IP3R1, inositol-1-tri-phosphate receptor 1; IRF3, interferon regulatory factor 3; LC3, microtubule-associated proteins 1A/1B light chain 3B; LPS, lipopolysaccharides; MAM, mitochondria-associated ER membrane; MCC, MAM Ca^{2+}-channeling complex; MEOS, microsomal ethanol oxidation system; MFF, mitochondrial fission factor; MFN1, mitofusin 1; MFN2, mitofusin 2; MiD49/MiD52, mitochondrial dynamics protein of 49 and 51 kDa; mPTP, mitochondrial transition pore; MQC, mitochondrial quality control; mtDAMPs, mitochondria-derived damage-associated molecular patterns; mtDepo, mitochondrial membrane depolarization; mtDNA, mitochondrial DNA; NAC, *N*-acetylcysteine; NADH, nicotinamide adenine dinucleotide (NAD) + Hydrogen (H); NF-κB, nuclear factor kappa B; NLR, nod-like receptor; NLRP3, NLR family pyrin domain-containing 3; NR4A1, nuclear receptor subfamily 4 group A member 1; NRF-1, nuclear respiratory factor-1; OMM, outer mitochondrial membrane; OPA1, optic atrophy 1; p53, tumor protein P53; p62, ubiquitin-binding protein p62; PAMPs, pathogen-associated molecular patterns; PDK4, pyruvate dehydrogenase kinase; PERK, protein kinase RNA-like ER kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PINK1, PTEN-induced kinase 1; PP, periportal; PV, perivenous; ROS, reactive oxygen species; SHC, Src homology and collagen; SIRT1, sirtuin 1; STING, stimulator of interferon (IFN) genes; TCA, tricarboxylic acid cycle; TFAM, mitochondrial transcription factor A; TFEB, transcription factor EB; TLR4, toll-like receptor 4; UQCRC2, ubiquinol-cytochrome C reductase core protein 2; VDAC, voltage-dependent anion channel.

liver damage and inflammation. Preserving mitochondrial health presents a promising therapeutic approach to mitigate ALD progression. In this review, we provide a comprehensive overview of the effects of alcohol on mitochondrial function and quality control mechanisms, highlighting their role in ALD pathogenesis. Understanding these mechanisms may pave the way for the development of novel therapeutic interventions for ALD.

Keywords: Alcohol-Associated Liver Disease, Mitochondrial, Dysfunction, Mitochondrial Quality Control

INTRODUCTION

Alcohol-associated liver disease (ALD) encompasses a spectrum of histopathological disorders, ranging from hepatic steatosis to severe conditions such as alcoholic hepatitis, fibrosis, cirrhosis, and HCC.[1,2] The pathogenesis of ALD is complex, and effective therapeutic options are limited. Understanding the key factors involved in ALD development is crucial for identifying potential therapeutic targets.

Mitochondria, essential organelles responsible for cellular energy production, redox balance, and metabolic processes, play a pivotal role in alcohol metabolism.[3–6] They are particularly vulnerable to alcohol-induced damage due to their involvement in the conversion of acetaldehyde to acetate during alcohol metabolism.[3–6] Prolonged alcohol consumption overwhelms detoxification mechanisms, leading to mitochondrial dysfunction and subsequent hepatocellular injury.[4]

Mitochondria maintain their optimal function through mitochondrial quality control (MQC) checkpoints, which include biogenesis, dynamics, and mitophagy.[7] Impaired mitochondrial MQC results in decreased ATP production and excessive reactive oxygen species (ROS), leading to energy depletion and compromised essential cellular processes, thereby triggering hepatic steatosis.[8,9] Alcohol-induced mitochondrial dysfunction disrupts mitochondrial fatty acid oxidation and cellular lipid homeostasis, contributing to hepatic steatosis.[10,11] In addition, alcohol-induced mitochondrial dysfunction activates inflammatory pathways, leading to the release of proinflammatory cytokines, exacerbating liver damage and disease progression.[12,13] Mitochondrial dysfunction also promotes apoptosis by disrupting the balance between proapoptotic and antiapoptotic factors in ALD.[14] Persistent deterioration of mitochondrial health and structural integrity causes hepatocyte damage, activation of HSCs, and fibrogenesis, leading to liver fibrosis and, ultimately, cirrhosis, further compromising liver function.[15,16]

The importance of maintaining mitochondrial health has garnered significant attention as a potential avenue for therapeutic interventions to mitigate ALD progression.[17–22] Therefore, understanding the role of mitochondrial dysfunction in ALD is crucial for unraveling underlying mechanisms and identifying potential therapeutic targets. This review explores recent findings on the effects of alcohol on mitochondrial function and quality control, providing a comprehensive understanding of the implications of mitochondrial dysfunction in ALD.

Role of mitochondria in alcohol metabolism

Alcohol (ethanol) is primarily metabolized in the liver.[6] Alcohol dehydrogenase (ADH), a cytosolic enzyme, initiates ethanol metabolism by converting it into acetaldehyde. Acetaldehyde is then further metabolized into acetate by acetaldehyde dehydrogenase 2 (ALDH2), an enzyme predominantly expressed in mitochondria.[6] Alcohol metabolism, particularly through ADH and ALDH2, generates nicotinamide adenine dinucleotide (NAD) and hydrogen (H) (NADH) by reducing the coenzyme NAD^+.[6] In addition, the microsomal ethanol oxidation system (MEOS), catalase, and cytochrome P450 family 2 subfamily E member 1 (CYP2E1) also contribute to the conversion of alcohol to acetaldehyde.[6] Specifically, the CYP2E1 pathway uses protons (H^+) from NADPH and oxygen (O_2), leading to electron leakage that partially reduces oxygen and produces ROS, such as superoxide anion radicals (O2•−) and hydrogen peroxide (H_2O_2).[23,24]

NADH plays a vital role in cellular respiration by participating in the mitochondrial electron transport chain (ETC) through complex I, contributing to ATP production.[25,26] Despite its role in ATP production, alcohol metabolism negatively impacts mitochondrial energy production by depleting NAD^+ levels and increasing NADH levels.[27,28] The elevated NADH/NAD^+ ratio inhibits the oxidation of other mitochondrial substrates, such as fatty acids and glucose, thereby reducing ATP production.[29] Acetate from alcohol metabolism is converted into acetyl-CoA by acetyl-CoA synthetase, which then enters the tricarboxylic acid cycle (TCA) to produce citrate.[10] Citrate is transported out of the mitochondria into the cytosol through the mitochondrial citrate carrier (SLC25A1), where it undergoes a series of enzymatic reactions involving ATP

citrate lyase (ACLY) and acetyl-CoA carboxylase (ACC) to form malonyl Coenzyme A (malonyl-CoA).[30] Malonyl-CoA inhibits carnitine palmitoyl transferase 1 (CPT1), a crucial enzyme for transporting fatty acids into the mitochondria.[31] Ethanol exposure also suppresses AMP-activated protein kinase (AMPK) activity, which further increases ACC activity and raises malonyl-CoA levels.[32] Interestingly, ethanol enhances the sensitivity of CPT1 to malonyl-CoA.[33] Consequently, reduced CPT1 activity further diminishes mitochondrial β-oxidation, promoting de novo lipogenesis and contributing to lipid accumulation in hepatocytes.[34,35] Overall, alcohol decreases the capacity of mitochondrial fatty acid oxidation, disrupting cellular energy balance and contributing to the development of hepatic steatosis (Figure 1A).

Mitochondrial dysfunction as a contributing factor in the pathogenesis of ALD

Previous studies have highlighted the detrimental impact of alcohol on mitochondrial function and structure, contributing to the development of ALD.[19,36,37] Mitochondrial calcium (Ca^{2+}) accumulation has been identified as a factor promoting alcohol-induced mitochondrial dysfunction in ALD.[37–39] Acetaldehyde, an intermediate in alcohol metabolism, rapidly affects mitochondrial membrane potential ($\Delta\Psi m$) in hepatocytes.[40] The $\Delta\Psi m$, dependent on proton pumps (Complexes I, III, and IV), is crucial for oxidative phosphorylation and ATP synthesis.[41] The effect of alcohol on $\Delta\Psi m$ occurs within hours of post-alcohol exposure, peaking between 6 and 12 hours and affecting up to 94% of hepatocytes.[40] Furthermore, alcohol disrupts the function of ETC, which is essential for electron flow and oxidative phosphorylation, compromising mitochondrial ATP production.[42] Alcohol also alters the expression of ETC complex proteins, leading to reduced mitochondrial oxygen consumption rate in mouse hepatocytes.[18,43]

In alcohol-induced steatohepatitis, activating transcription factor 4 (ATF4) activation in hepatocytes impairs mitochondrial biogenesis and respiratory function.[43] ATF4 negatively regulates mitochondrial transcription factor A (TFAM) by repressing nuclear respiratory factor-1 (NRF-1) transcription, leading to mitochondrial stress and contributing to alcohol-induced

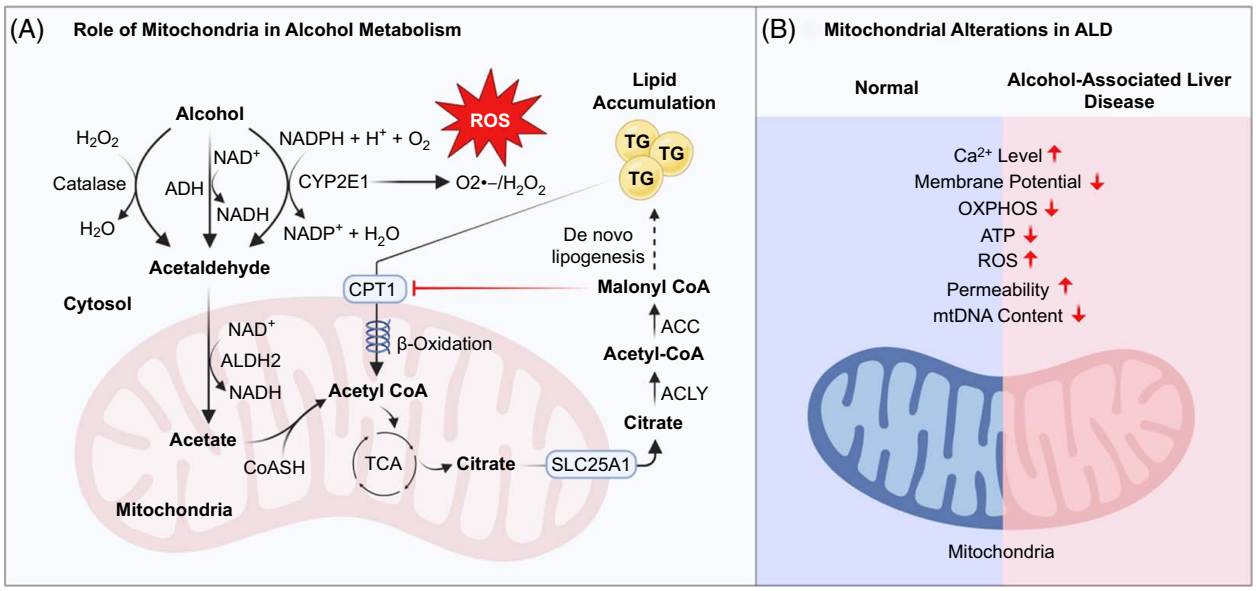

FIGURE 1 Alcohol metabolism in mitochondria and mitochondrial changes in alcohol-related liver disease. (A) In hepatocytes, alcohol is primarily metabolized by ADH enzymes to form acetaldehyde. Acetaldehyde is then further metabolized into acetate by ALDH2 enzymes, primarily located in the mitochondria. This conversion of acetaldehyde to acetate generates NADH by reducing the coenzyme NAD^+. In addition, the MEOS, catalase, and CYP2E1 enzymes also play a role in converting alcohol to acetaldehyde. However, the CYP2E1 pathway generates ROS such as superoxide anion radicals (O2•−) and hydrogen peroxide (H_2O_2), contributing to oxidative stress in hepatocytes. Acetate is further metabolized into acetyl-CoA to form citrate in the TCA cycle. The elevation in citrate levels drives malonyl-CoA production through the mitochondrial citrate carrier (SLC25A1), ATP citrate lyase (ACLY), and ACC enzymes. This process ultimately inhibits CPT1, an enzyme involved in the transport of fatty acids into the mitochondria for β-oxidation. As a result, the inhibition of CPT1 reduces mitochondrial β-oxidation, leading to the accumulation of TGs and alcohol-induced steatosis. (B) Key features of alcohol-induced mitochondrial dysfunction include Ca^{2+} accumulation, loss of membrane potential ($\Delta\Psi m$), disrupted ETC function leading to reduced mitochondrial oxidative phosphorylation and ATP production, along with increased formation of ROS. Ultimately, this results in damage and decreased mtDNA content, causing mitochondrial membrane permeability and leading to cell death in ALD. Abbreviations: ACC, acetyl-CoA carboxylase; ADH, alcohol dehydrogenase; ALDH2, aldehyde dehydrogenase 2; CoASH, Coenzyme A; CPT1, carnitine palmitoyl transferase 1; CYP2E1, cytochrome P450 2E1; ETC, electron transport chain; MEOS, microsomal ethanol oxidation system; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; TG, triglyceride.

steatohepatitis.[43] Chronic ethanol intake increases mitochondrial Ca^{2+} levels and oxidative stress and sensitizes liver mitochondria to mitochondrial permeability transition pore (mPTP) opening.[37]

Overall, alcohol impairs mitochondrial function by increasing oxidative stress, depleting mtDNA, and causing mitochondrial membrane permeabilization, ultimately leading to liver injury[44,45] (Figure 1B). These findings underscore the importance of understanding the molecular mechanisms underlying alcohol-induced mitochondrial dysfunction in ALD pathogenesis.

Impaired MQC in ALD

MQC is a vital process that ensures the maintenance of optimal mitochondrial function and homeostasis. MQC encompasses multiple checkpoints, including mitochondrial biogenesis, regulation of mitochondrial bioenergetics through ER-mitochondria interactions, dynamics, and mitophagy.[7] In ALD, several MQC checkpoints have been observed to be defective.[46–49] Chronic alcohol consumption disrupts the delicate balance of mitochondrial fusion-fission dynamics and promotes excessive production of ROS.[36,48,50] Excessive ROS generation not only damages mitochondria but also impedes their self-repair mechanisms, including mitophagy.[46] The impaired MQC leads to the accumulation of dysfunctional mitochondria in hepatocytes, promoting oxidative stress, energy depletion, and inflammation, which are key distinctive features of ALD.[51]

Mitochondrial biogenesis

Mitochondrial biogenesis, the process of generating new mitochondria in cells, undergoes significant alterations in ALD.[43,52] Chronic alcohol use directly and indirectly impacts mitochondrial biogenesis in the liver. Alcohol directly induces the degradation of hepatic mtDNA[53] and disrupts nuclear transcription factors, including peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) and NRF-1, crucial factors involved in mitochondrial biogenesis.[43,52] ROS generated during alcohol metabolism deplete mtDNA and diminish the capacity for mitochondrial biogenesis.[39,43] Alcohol-induced endoplasmic reticulum (ER) stress signaling, specifically the protein kinase RNA-like ER kinase (PERK)-eIF2α-ATF4 pathway, influences mitochondrial biogenesis by repressing NRF-1 transcriptional activity, leading to suppression of TFAM, a protein responsible for mitochondrial DNA replication.[43,54] Hepatocyte-specific overexpression of TFAM reinstates mitochondrial biogenesis and protects against alcohol-induced mitochondrial dysfunction.[43] Chronic ethanol feeding in mice induces hyperacetylation of PGC-1α, suppressing its transcriptional activity and reducing mitochondrial biogenesis.[55,56] Moreover, reduced Sirtuin 1 (SIRT1) activity, due to an increased NADH to NAD^+ ratio in alcohol-fed mice, contributes to decreased PGC-1α deacetylation, hampering mitochondrial DNA replication and biogenesis.[56] However, replenishing cellular NAD^+ levels with nicotinamide riboside restored mitochondrial biogenesis through activation of the SIRT1-PGC-1α pathway, ultimately preventing alcohol-induced liver injury in a chronic-plus-binge ethanol feeding mouse model of ALD.[52]

Conversely, some studies have shown that intragastric alcohol feeding stimulates increased respiration accompanied by upregulation of PGC-1α and enhanced mitochondrial biogenesis.[49] Furthermore, oral alcohol feeding in mice causes less liver injury and demonstrates a mild increase in mitochondrial respiration, potentially indicating adaptive responses to alcohol metabolism.[49] Together, these findings suggest that liver mitochondrial plasticity is observed in response to alcohol-induced metabolic stress, potentially serving as an adaptive mechanism to prevent hepatotoxic effects during the early stages of ALD (Figure 2A).

Regulation of mitochondrial bioenergetics through ER-mitochondria interactions

Both acute and chronic alcohol exposure induce the release of Ca^{2+} from internal stores, particularly the ER in hepatocytes.[57] The released cytosolic Ca^{2+} is absorbed by mitochondria, resulting in increased mitochondrial Ca^{2+} levels in the hepatocytes of alcohol-fed rats compared to controls.[38] Mitochondria-associated ER membranes (MAMs), an interface between mitochondria and the ER within an approximate distance of 10–50 nm, play a crucial role in regulating Ca^{2+} transport from the ER to mitochondria to support mitochondrial metabolism and respiration.[58] The MAM Ca^{2+}-channeling (MCC) complex, consisting of glucose-regulated protein 75 (GRP75), inositol-1-triphosphate receptor 1 (IP3R1), and voltage-dependent anion channel 1 (VDAC1), regulates Ca^{2+} transfer in the MAM.[59] GRP75 functions as a tether facilitating ER-mitochondria interaction to efficiently transport Ca^{2+} to the mitochondria by physically interacting with the ER Ca^{2+} efflux channel, IP3R1, and the outer mitochondrial membrane (OMM) protein, VDAC1.[60,61] In normal conditions, ER-mitochondria interaction through MAMs serves as a crucial mechanism for regulating Ca^{2+} homeostasis and energy production. However, aberrant MAM formation, leading to excessive Ca^{2+} accumulation in mitochondria, impairs mitochondrial function and contributes to oxidative stress and cell death.[60]

The dysregulation of mitochondrial Ca^{2+} and perturbation of ER-mitochondria interactions have profound

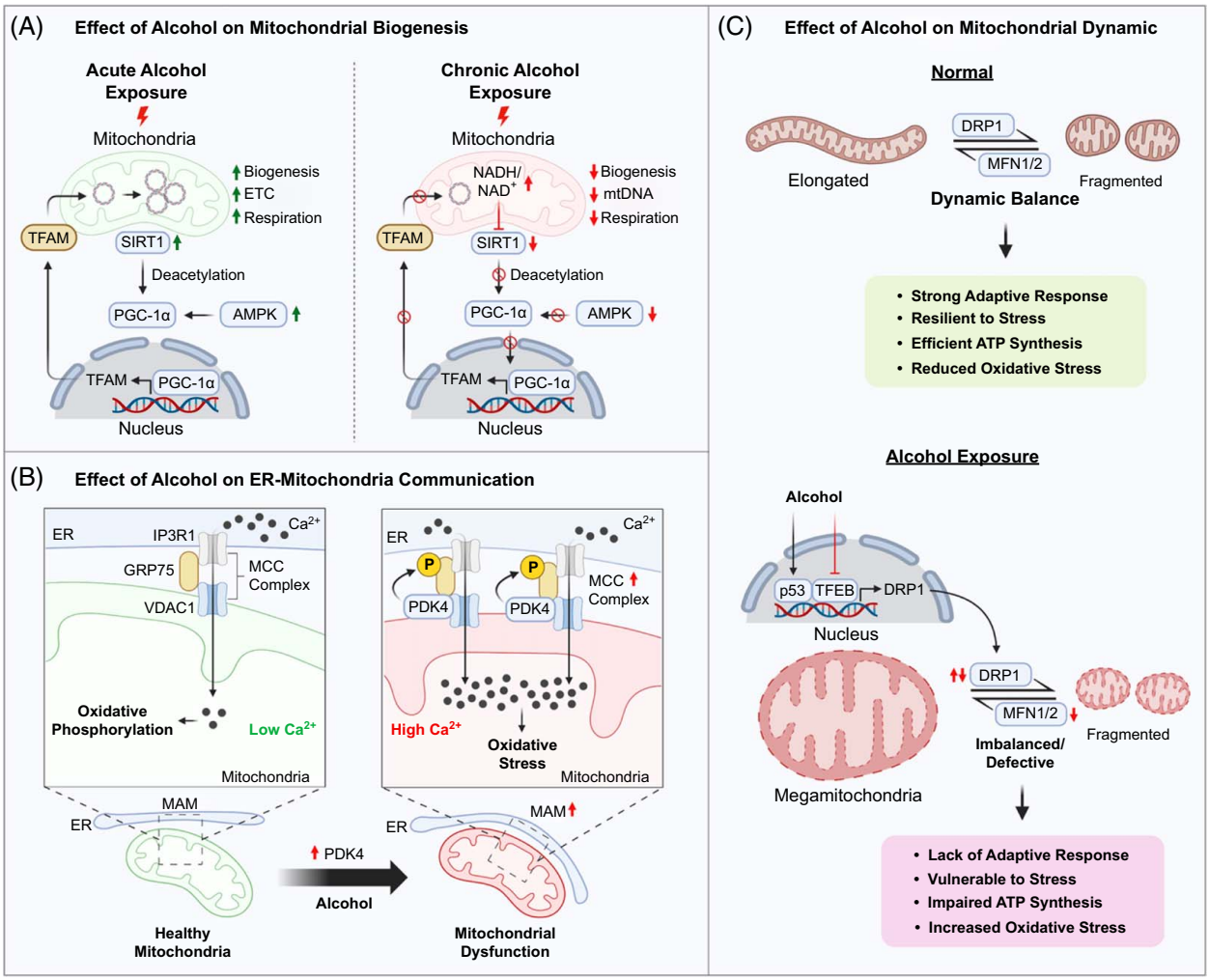

FIGURE 2 Effect of alcohol on mitochondrial biogenesis, ER-mitochondria communication, and mitochondrial dynamics. (A) Acute alcohol exposure initially stimulates mitochondrial biogenesis, resulting in increased expression of components of the mitochondrial ETC and enhancing respiration. This response is associated with the upregulation of key factors like PGC-1α–mediated TFAM, which is required for mitochondrial DNA amplification. This process is facilitated by its upstream regulators, SIRT1 and AMPK, leading to enhanced mitochondrial function. However, chronic alcohol exposure disrupts mitochondrial biogenesis due to an increased NADH/NAD$^+$ ratio, which results in a decline in SIRT1 activity and reduced AMPK activity, impairing the PGC-1α pathway. This ultimately leads to mitochondrial dysfunction in ALD. (B) Under normal conditions, the interaction between the ER and mitochondria through MAMs is critical for maintaining low Ca^{2+} levels and supporting mitochondrial function. In the MAM, the transfer of Ca^{2+} is regulated by the MCC complex, which includes proteins such as GRP75, IP3R1, and VDAC1. GRP75 facilitates ER-mitochondria interaction and Ca^{2+} transfer. However, exposure to alcohol increases the expression of PDK4. This increase in PDK4 induces phosphorylation of GRP75, resulting in increased formation of MAMs and the MCC complex, promoting alcohol-induced mitochondrial Ca^{2+} accumulation and dysfunction. (C) Mitochondrial dynamics involve fission through DRP1, and fusion controlled by MFN1 and MFN2 to maintain mitochondrial dynamic balance and optimize function. Alcohol disrupts this balance, leading to structural changes such as megamitochondria and fragmented mitochondria. Increased megamitochondria result from reduced DRP1 expression caused by decreased TFEB activation, along with reduced MFN1 and MFN2 expression. However, alcohol also stimulates the p53-mediated induction of DRP1 expression, exacerbating mitochondrial fission and contributing to mitochondrial dysfunction in ALD. Abbreviations: ALD, alcohol-associated liver disease; AMPK, AMP-activated protein kinase; DRP1, dynamin-related protein 1; ER, endoplasmic reticulum; ETC, electron transport chain; GRP75, glucose-regulated protein 75; IP3R1, inositol-1-tri-phosphate receptor 1; MAM, mitochondria-associated ER membranes; MCC, MAM Ca^{2+}-channeling; MFN, mitofusin; PDK4, pyruvate dehydrogenase kinase 4; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; SIRT1, Sirtuin 1; TFAM, mitochondrial transcription factor A; TFEB, transcription factor EB; VDAC1, voltage-dependent anion channel 1.

implications for liver function and can contribute to the pathogenesis of ALD.[59] Alcohol promotes Ca^{2+} release from the ER, leading to an overload of mitochondrial Ca^{2+} through increased MCC complex formation.[59] Pyruvate dehydrogenase kinase 4 (PDK4) plays a key role in promoting MCC complex formation in ALD by phosphorylating GRP75 at multiple sites (Threonine 120, Serine 266, and Threonine 267), facilitating MCC complex formation[59] (Figure 2B). Genetic ablation of PDK4 or mutation of GRP75 phosphorylation sites prevents alcohol-induced MCC complex formation, mitochondrial Ca^{2+} accumulation, and mitochondrial dysfunction.[59] In addition, enhancing MAM formation with a synthetic ER-mitochondria linker reverses the

protective effect of PDK4 deficiency in alcohol-induced liver injury.[59] These observations suggest that dysregulation of mitochondrial Ca^{2+} through abnormal increases in MAM and MCC complex formation plays a significant role in promoting mitochondrial dysfunction during ALD pathogenesis.

Mitochondrial dynamics

Mitochondrial dynamics involve coordinated fission and fusion cycles to maintain optimal mitochondrial function.[62] Fission is facilitated by dynamin-related protein 1 (DRP1), which is recruited to mitochondria by receptor proteins at the OMM, such as mitochondrial fission 1 (FIS1), mitochondrial fission factor (MFF), mitochondrial dynamics protein of 49 and 51 kDa (MiD49 and MiD51), FUN14 domain containing 1 (FUNDC1), and Septin2.[62,63] Fusion, on the other hand, involves mitofusins (MFNs), which control OMM fusion, and optic atrophy 1 (OPA1), which assists in inner mitochondrial membrane (IMM) fusion.[58] The loss of fission or fusion components disrupts mitochondrial dynamics and impairs mitochondrial function.[64]

Alcohol disrupts mitochondrial dynamics equilibrium, leading to structural and functional changes.[21] Ultrastructural changes, such as the presence of megamitochondria, are considered hallmarks of ALD severity and predict mortality risk.[47,65] Experiments using primary hepatocytes isolated from control or ethanol-fed rats revealed that normal hepatocytes exhibit slow mitochondrial dynamics.[36] Similarly, prolonged ethanol exposure in VL-17A cells, a hepatoma cell line with ADH and CYP2E1 activities, led to reduced mitochondrial dynamics, indicating a negative impact of alcohol on mitochondrial fusion in hepatocytes.[36]

Insufficient mitochondrial dynamics not only impairs energy production but also contributes to oxidative stress, inflammation, and damage to hepatocytes in ALD.[51] A study using human liver slices treated with ethanol to model early ALD found a mild increase in DRP1 expression and its translocation to mitochondria, along with increased levels of MiD51.[48] However, in patients with alcoholic hepatitis (AH), there was a significant increase in DRP1 expression and its translocation to mitochondria, accompanied by higher expression of other fission factors such as MFF, FIS1, and MiD51, indicating that mitochondrial fission intensifies with disease severity.[48] In addition, overexpression of an inactive Drp1 mutant prevented ethanol-induced growth impairment in VL-17A cells, while liver-specific DRP1 knockout mice exhibited increased megamitochondria formation and reduced alcohol-induced liver injury.[66] A clinical study suggests that detecting megamitochondria in liver biopsies is associated with improved survival in patients with AH.[67] These findings suggest that inhibiting DRP1 to enhance mitochondrial fusion may help mitigate alcohol-induced hepatotoxicity.

Furthermore, in chronic alcohol-fed mice, upregulated DNA-dependent protein kinase catalytic subunit (DNA-PKcs) was found to enhance the expression of the DRP1 gene by activating the tumor protein P53 (p53), promoting mitochondrial fission and mitochondrial dysfunction in hepatic tissue.[39] Liver-specific deletion of DNA-PKcs suppressed DRP1-mediated mitochondrial fission and prevented alcohol-induced mitochondrial dysfunction and cytoxicity.[39] Orphan nuclear receptor subfamily 4 group A member 1 (NR4A1) acts upstream of DNA-PKcs activation, and genetic ablation of NR4A1 has a protective effect similar to DNA-PKcs knockout, ameliorating ALD.[39] Conversely, another study showed that reduced hepatic DRP1 levels led to megamitochondria formation, associated with alcohol-induced mitochondrial maladaptation through downregulation of the transcription factor EB (TFEB) in both samples of patients with AH and a chronic-plus-binge ethanol feeding mouse model.[51] Notably, in this study, besides the reduction in DRP1, mitochondrial fusion proteins MFN1 and MFN2 were also significantly reduced, indicating impairment of both fusion and fission dynamics[51] (Figure 2C). In the liver, the metabolic zonation categorizes hepatocytes according to their functions based on anatomical locations such as perivenous (PV) and periportal (PP) zones.[68] The PV zone is most sensitive to chronic alcohol intake due to the higher expression of CYP2E1.[69] Alcohol consumption increases the number of mitochondria, especially in the PV zone, where mitochondria are shorter in length compared to those in the PP region.[70] Mice on an alcohol diet exhibited reduced mitochondrial perimeter in PV hepatocytes, while PP hepatocytes displayed an increased mitochondrial perimeter, similar to previous reports of alcohol-induced megamitochondria formation.[51,59,65] The findings suggest that alcohol affects mitochondrial shape and size differently across various liver zones. The differences in mitochondrial dynamics between PV and PP hepatocytes imply that these zonal populations may respond differently to alcohol exposure, underscoring the complexity of alcohol's impact on mitochondrial dynamics. Further research is necessary to fully elucidate these effects.

Mitophagy

Mitophagy, the process by which damaged mitochondria are selectively removed, involves 2 main pathways: ubiquitin-mediated and receptor-mediated mitophagy.[71] In ubiquitin-mediated mitophagy, PINK1 recruits Parkin to damaged mitochondria, tagging them with ubiquitin. The ubiquitin-binding protein p62 (p62) then recognizes these tags, facilitating their delivery to autophagosomes

for selective degradation through the autophagic process.[71] In receptor-mediated mitophagy, proteins such as FUNDC1 on the OMM recognize damaged mitochondria, marking them for engulfment and degradation by interacting with microtubule-associated proteins 1A/1B light chain 3B (MAP1LC3B), also known as LC3, on autophagosomal membranes.[72]

Acute alcohol exposure causes rapid mitochondrial membrane depolarization (mtDepo) in mouse hepatocytes, triggering a PINK1-Parkin mitophagy response.[73] Acetaldehyde, a product of alcohol metabolism, is identified as a crucial factor promoting mtDepo.[40] Mitophagy is observed to occur in a dose-dependent manner with alcohol, as evidenced by increased autophagic markers, mitochondrial PINK1 and Parkin expression, and green fluorescent protein–labeled LC3 (GFP-LC3) puncta around mitochondria after alcohol treatment, indicating enhanced mitophagy.[40,73] Excessive alcohol intake enhances the formation of megamitochondria.[47] Excessive alcohol intake leads to the formation of megamitochondria, which impairs the removal of damaged mitochondria, resulting in the accumulation of defective mitochondria and increased oxidative stress.[74] This accumulation disrupts the maintenance of a healthy mitochondrial population essential for proper cellular energy production in hepatic tissue and exacerbates inflammation, increasing susceptibility to alcohol-induced damage.[46,75]

Alcohol feeding in Parkin-deficient mice results in severe mitochondrial damage, oxidative stress, impaired mitophagy, compromised β-oxidation, reduced mitochondrial respiration, and decreased cytochrome c oxidase activity compared to wild-type (WT) mice.[76] These observations underscore the critical role of Parkin-mediated mitophagy in mitigating alcohol-induced mitochondrial damage, steatosis, and liver injury.[76] Activation of AMPK by metformin restores the expression of ubiquinol-cytochrome c reductase core protein 2 (UQCRC2), a component of the mitochondrial ETC, which was reduced by alcohol exposure in a 10-day ethanol-fed mouse model of ALD.[77] In addition, knockdown of UQCRC2 impairs Parkin recruitment to the mitochondria and disrupts mitophagy, whereas overexpression of UQCRC2 enhances Parkin-mediated mitophagy and mitigates liver injury.[77] AMPK indirectly increases UQCRC2 expression through the activation of the NRF2 pathway.[77] The study further highlights that UQCRC2 independently regulates mitophagy without affecting the overall function of the ETC.[77] In addition, administration of tetramethylpyrazine (TMP), an extract from *Ligusticum wallichii* Franch, promotes mitophagy through the PINK1/Parkin pathway by restoring UQCRC2 expression, thereby providing protection against alcohol-induced liver injury, inflammation, and ROS overproduction.[78] Collectively, these findings suggest that restoring UQCRC2 expression may be beneficial for enhancing Parkin-mediated mitophagy to protect against ALD.

Chronic alcohol consumption has been shown to suppress FUNDC1-dependent mitophagy through the upregulation of DNA-PKcs.[39] This process involves DNA-PKcs–mediated activation of p53, which in turn upregulates casein kinase 2 (CK2) expression. CK2 subsequently phosphorylates FUNDC1 at Serine 13, inhibiting mitophagy.[39] This impairment in mitophagy leads to mitochondrial dysfunction, hepatic apoptosis, and progression of ALD.[39] These findings suggest that compromised ubiquitin-mediated and receptor-mediated mitophagy significantly contribute to the pathogenesis of ALD. Acute alcohol exposure has been shown to increase the transcriptional activity of TFEB, a key regulator of autophagy and lysosomal biogenesis, which is accompanied by increased LAMP1 expression and lysosomal processing.[73] This facilitates the removal of damaged mitochondria through mitophagy and may serve as an adaptive response to protect mitochondria against acute alcohol exposure. However, chronic alcohol exposure downregulates TFEB expression, disrupting the mitophagy pathway by impairing autophagosome and lysosomal biogenesis.[51,79] This shift in the mitochondrial adaptation pathway toward maladaptive processes results in the accumulation of dysfunctional mitochondria, driving the progression of ALD[51,79] (Figure 3A).

mPTP and cell death in ALD

The opening of the mPTP occurs when the mitochondrial membrane becomes permeable, triggered by factors such as increased Ca^{2+} levels and oxidative stress.[80] mPTP opening allows the release of mitochondrial components, including proapoptotic factors like cytochrome C, into the cytosol, initiating the apoptotic process.[80] Studies have indicated that chronic alcohol consumption leads to increased mitochondrial Ca^{2+} levels and oxidative stress, promoting mPTP opening and hepatocyte cell death, consequently causing liver injury.[19,37,81] Mitochondria isolated from the livers of ethanol-exposed rats exhibit diminished mitochondrial Ca^{2+} retention capacity (the threshold level of mitochondrial Ca^{2+} required to induce mPTP opening) alongside an increased presence of the proapoptotic BAX protein in the mitochondria and upregulation of cyclophilin D (CypD), key factors involved in mPTP opening and apoptosis.[37] Notably, acute ethanol exposure triggers BAX translocation to mitochondria, where BAX associates with the mitochondrial VDAC and induces hepatocyte apoptosis.[82] However, inhibition of BAX-VDAC interactions using anti-VDAC antibody effectively mitigated ethanol-induced hepatocyte apoptosis, highlighting the critical role of BAX-VDAC interaction in mPTP pore opening and hepatic cell death in alcohol-induced liver injury.[82]

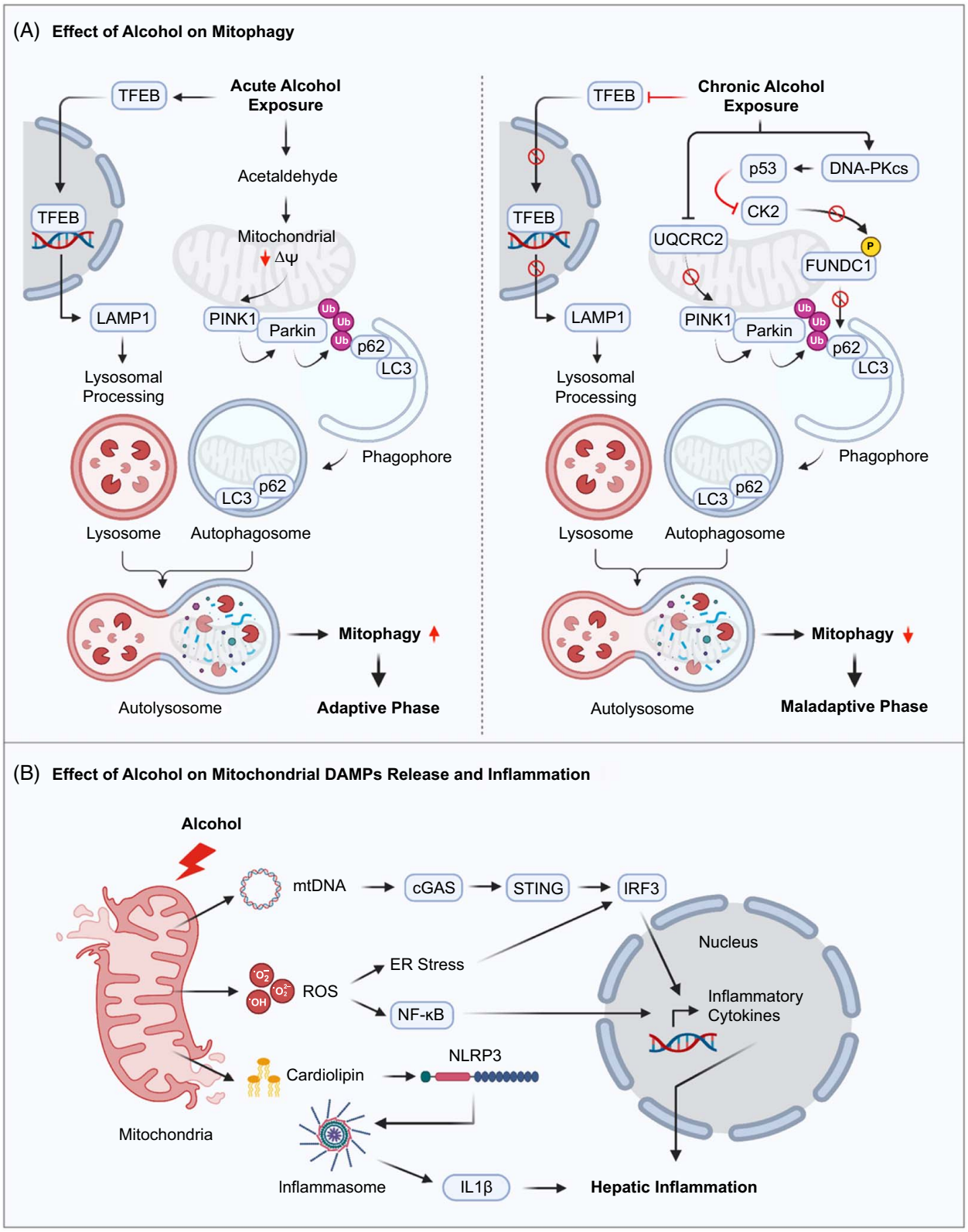

FIGURE 3 Effect of alcohol on mitophagy, mitochondrial DAMPs release, and inflammation. (A) During acute alcohol exposure, acetaldehyde decreases mitochondrial membrane potential ($\Delta\psi$), initiating PINK1-Parkin-mediated ubiquitination and recruitment of phagophores containing LC3-p62 proteins, facilitating mitophagy for the removal of damaged mitochondria. In addition, acute alcohol exposure induces TFEB-mediated LAMP1 expression, enhancing lysosomal processing and inducing mitophagy as an adaptive response. Conversely, chronic alcohol exposure downregulates UQCRC2, inhibiting Parkin-mediated mitophagy, increases DNA-PKcs levels, activating p53, and inhibiting CK2-mediated FUNDC1 phosphorylation, thus hindering receptor-mediated mitophagy. Chronic alcohol exposure also disrupts TFEB, leading to the accumulation of dysfunctional mitochondria and contributing to maladaptive mitochondrial dysfunction in ALD. (B) Alcohol-induced mitochondrial damage

releases mtDAMPs such as mtDNA, Cardiolipin, and ROS, which trigger inflammasome activation and sterile inflammation. The presence of mtDNA in the cytoplasm activates the cGAS-STING-IRF3 pathway, inducing an inflammatory response. Excessive mitochondrial ROS production induces ER stress and activates NF-kB, leading to inflammatory cytokine production. Furthermore, exposure to Cardiolipin, a mitochondrial inner membrane component, promotes inflammasome formation and the release of proinflammatory cytokines such as IL-1β, thereby contributing to liver inflammation in ALD. Abbreviations: ALD, alcohol-associated liver disease; DAMP, damage-associated molecular pattern; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; ER, endoplasmic reticulum; mtDAMP, mitochondria-derived damage-associated molecular pattern; ROS, reactive oxygen species; TFEB, transcription factor EB; UQCRC2, ubiquinol-cytochrome c reductase core protein 2.

mtDAMPS in ALD

Damage-associated molecular patterns (DAMPs) are molecules released by damaged cells, leading to inflammation and tissue damage.[83] Mitochondria are a significant source of DAMPs, referred to as mitochondria-derived damage-associated molecular pattern (mtDAMPs).[84] These include mtDNA, TFAM, cardiolipin, cytochrome C, ROS, succinate, and *N*-formyl peptides released from damaged mitochondria, promoting sterile inflammation by activating inflammasomes and pattern recognition receptors in nonparenchymal cells, thereby contributing to a spectrum of ALD.[84,85]

Alcohol-induced mitochondrial injury has been shown to release mtDNA into the cytoplasm.[86] In alcohol-fed mice, elevated levels of cytoplasmic mtDNA have been observed.[86] The presence of mtDNA in the cytosol is detected by the dsDNA sensor, cyclic GMP-AMP synthase (cGAS), which promotes the production of the secondary messenger 2′3′-cyclic GMP-AMP (cGAMP).[87] cGAMP further activates the STING pathway, triggering an inflammatory response by activating interferon regulatory factor 3 (IRF3) and NF-κB, crucial transcription factors governing innate immune responses.[87] The increase in cytosolic DNA induced by alcohol activates the IRF3 signaling pathway through a cGAS-STING–dependent mechanism, promoting inflammation and hepatocyte apoptosis.[86] This activation spreads from alcohol-injured hepatocytes to neighboring cells through gap junction intercellular communication facilitated by connexin 32 (Cx32), amplifying IRF3 activation across cells.[86] However, hepatocyte-specific knockout of cGAS or STING prevents alcohol-induced IRF3 activation, protecting against liver injury in mice.[86] This suggests that mtDAMPs play a mediating role in aggravating ALD pathogenesis. In addition, alcohol-induced megamitochondria formation promotes mtDNA release into the cytosol and serum, activating the cGAS-STING-IRF3/7 pathway and inducing an inflammatory immune response.[51] Chronic alcohol exposure induces ER stress, promoting the release of mtDNA-enriched microparticles from hepatocytes.[88] This release subsequently results in inflammation, neutrophil infiltration, and liver injury.[88] Furthermore, alcohol-mediated excessive generation of mitochondrial ROS also functions as mtDAMPs, inducing hyperactivation of the nod-like receptor (NLR) family pyrin domain-containing 3 (NLRP3), leading to hypersecretion of IL-1β and causing hepatic inflammation.[13]

In alcoholic hepatitis (AH), the induction of Src homology and collagen (SHC), a major adapter protein regulating tyrosine kinase receptors, was positively associated with serum ALT levels in a mouse model of chronic-plus-binge alcohol diet–induced liver injury.[89] The mitochondrial p46Shc isoform inhibits fatty acid β-oxidation, suggesting a link between SHC induction and altered lipid metabolism. Inhibition of fatty acid β-oxidation leads to the activation of eukaryotic translation initiation factor 2 subunit α (eIF2α).[89] SHC induction is associated with preapoptotic signals involving caspase-8 and B-cell receptor-associated protein 31 (BAP31) cleavage, ultimately resulting in Bcl-2 homologous antagonist/killer (BAK) and BCL-2 associated X (BAX) activation, which plays a role in the apoptotic process.[89] The activated events trigger the translocation of Calreticulin/ER protein 57 (CRT/ERp57) complexes from the ER to the cell membrane.[89] CRT/ERp57 complexes act as DAMPs on the cell membrane, inducing an inflammatory response.[89] Overall, these studies emphasize that mtDAMPs play a vital role in promoting sterile inflammation, linking them to inflammatory processes, hepatocyte apoptosis, and liver injury induced by chronic alcohol exposure (Figure 3B).

Impact of mitochondrial dysfunction on liver-gut interaction in inflammatory responses during ALD

The progression of ALD is influenced by complex interactions between the liver and gut, with mitochondrial dysfunction playing a central role in this interplay.[90,91] Mitochondria are vital for maintaining energy homeostasis in hepatic and intestinal cells.[8,92] Alcohol and its metabolite, acetaldehyde, impair mitochondrial function in these cells, leading to disrupted communication between the liver and gut and exacerbating inflammatory responses in ALD pathogenesis.[73,93,94] Chronic alcohol use has been linked to increased intestinal permeability, raising susceptibility to ALD.[95,96] In rats, chronic ethanol ingestion causes mitochondrial swelling, loss of matrix density, and dilated ER in ileal M cells of the intestinal epithelium, indicating mitochondrial stress.[97] In addition, alcohol induces mitochondrial dysfunction and ROS generation in rat gastric epithelial cells.[98] Both alcohol and acetaldehyde contribute to increased

intestinal permeability to endotoxins by inducing oxidative stress, disrupting intestinal tight junctions, and disassembling cytoskeleton proteins.[99–101] Mice deficient in ALDH2, a mitochondrial enzyme essential for acetaldehyde metabolism, exhibit exacerbated alcohol-induced dysfunction of intestinal epithelial cells, increased permeability, altered gut environment, and enhanced endotoxin release.[102,103] Moreover, acetaldehyde, produced in hepatocytes, is released into circulation and detoxified by gut ALDH2, underscoring the role of intestinal mitochondria in acetaldehyde metabolism.[104] Mitochondria-targeted ubiquinone (MitoQ), an antioxidant specifically designed to target mitochondria, mitigates acetaldehyde-induced disruption of intestinal tight junctions and reduces toll-like receptor 4 (TLR4)-mediated inflammatory responses in a mouse model of ALD, highlighting the importance of preventing mitochondrial dysfunction to protect against ALD.[22] However, the precise role of mitochondrial dysfunction in promoting ROS generation, acetaldehyde accumulation, and the subsequent dysfunction and permeability of intestinal epithelial cells in ALD remains unclear and warrants further investigation.

Elevated levels of serum pathogen-associated molecular patterns (PAMPs), such as endotoxin, lipopolysaccharides (LPS), and bacterial DNA, are recognized as key factors induced by alcohol consumption and involved in the pathogenesis of ALD.[105,106] Disruption of intestinal epithelial tight junctions significantly contributes to the increased release of PAMPs into circulation in ALD.[107] Circulating LPS triggers TLR4-mediated inflammasome activation in immune cells, such as KCs and macrophages, leading to the release of proinflammatory cytokines like TNF-α, IL-1β, and IL-18, which drive ALD progression.[85] In addition, alcohol-induced release of mtDNA from damaged hepatocytes triggers neutrophil accumulation in the liver and enhances KC activation.[88,108] Alcohol-mediated inhibition of autophagy results in the accumulation of defective mitochondria in macrophages, activating the inflammasome and promoting IL-1β production.[109] Furthermore, alcohol-induced CYP2E1 expression increases oxidative stress and shifts KCs and macrophages toward a proinflammatory phenotype, further exacerbating the inflammatory response and contributing to ALD progression.[110–113] Overall, these findings suggest that mitochondrial dysfunction plays a critical role in exacerbating inflammation during ALD development by creating a feedback loop between the liver and gut axis (Figure 4).

Future perspective on improving mitochondrial function to protect against ALD

The development of ALD involves complex interactions between various factors, signaling pathways, and cellular organelles, with mitochondrial dysfunction playing a prominent role.[21,114] Mitochondrial dysfunction is implicated in several stages of ALD progression, from steatosis to cirrhosis.[115] Research focusing on genetic manipulation and drug therapies aimed at improving mitochondrial function has shown promising results in protecting against ALD.[116,117] Therefore, targeting factors involved in modulating mitochondrial function emerges as a promising therapeutic strategy for ALD treatment. Mitochondrial function is regulated by checkpoint pathways such as mitochondrial biogenesis, dynamics, and mitophagy.[7] Impairment in these pathways can increase mitochondrial susceptibility to oxidative stress and dysfunction.[118] Previous studies have demonstrated that excessive alcohol intake disrupts these checkpoint pathways during ALD progression.[36,46,53] Future research could concentrate on developing interventions to enhance mitochondrial biogenesis, potentially targeting transcription factors like PGC-1α, NRF-1, and TFAM to promote the generation of new, functional mitochondria. Therapies aimed at modulating oxidative stress and restoring mitochondrial DNA replication capacity may also counteract the negative effects of chronic alcohol consumption on mitochondrial biogenesis. Strategies to improve MQC mechanisms, including mitophagy, could be explored. Enhancing mitophagy pathways might help selectively remove damaged mitochondria, thereby reducing oxidative stress, inflammation, and energy depletion associated with ALD. Future research may explore interventions targeting mitochondrial Ca^{2+} levels to restore Ca^{2+} homeostasis, reduce oxidative stress, and improve overall mitochondrial function in ALD.[38,59] Modulating mitochondrial dynamics could also be a promising strategy. Specifically targeting mitochondrial fission and fusion may help maintain optimal mitochondrial function and structure, thereby protecting against alcohol-induced mitochondrial dysfunction and liver damage.

Detecting mitochondrial dysfunction at the intracellular level can be challenging. In such cases, identifying reliable serum biomarkers capable of accurately assessing mitochondrial dysfunction could significantly aid in early disease prevention. Studies have shown that chronic ethanol-fed mice and individuals with excessive alcohol consumption exhibit elevated serum levels of mtDNA, which correlate with liver injury.[88,108] In addition, growth differentiation factor 15 (GDF-15) has been identified as a serum marker and potential diagnostic indicator for mitochondrial diseases.[119–121] GDF-15 has emerged as a prominent biomarker strongly associated with disease progression in ALD.[122,123] However, further research is needed to confirm its effectiveness specifically as a marker for mitochondrial dysfunction in ALD. Continued exploration is warranted to identify additional promising biomarkers for detecting mitochondrial dysfunction.

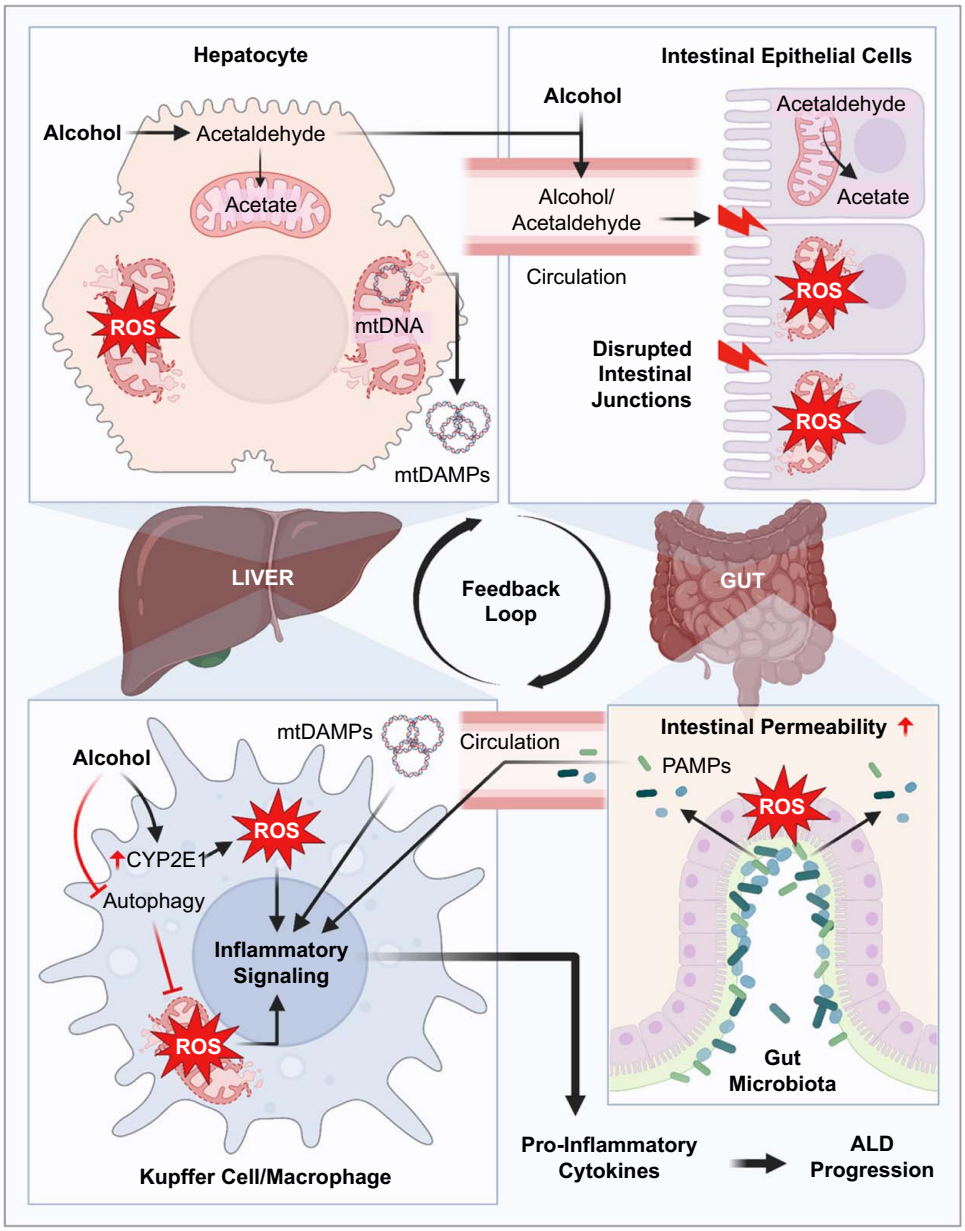

FIGURE 4 Effect of mitochondrial dysfunction on the liver-gut axis in triggering inflammatory responses in ALD. Alcohol is converted to acetaldehyde in hepatocytes and released into circulation, where it is detoxified by gut ALDH2. Under chronic conditions, both alcohol and acetaldehyde impair mitochondrial function, resulting in the release of mtDNA as DAMPs from hepatocytes and PAMPs from damaged intestinal junctions. Both DAMPs and PAMPs trigger an inflammatory response in hepatic immune cells, leading to the release of proinflammatory cytokines and creating a liver-gut feedback loop that exacerbates hepatic inflammation. In addition, alcohol-induced expression of CYP2E1 and inhibition of autophagy promote oxidative stress, leading to the transformation of KCs and macrophages into a proinflammatory phenotype, further intensifying the inflammatory response and contributing to the progression of ALD. Abbreviations: ALD, alcohol-associated liver disease; ALDH2, aldehyde dehydrogenase 2; CYP2E1, cytochrome P450 2E1; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular patterns.

Given the complexity of mitochondrial pathways involved in ALD pathogenesis,[44] a multitarget approach seems promising for future interventions. Combination therapies simultaneously targeting different aspects of mitochondrial function, including biogenesis, dynamics, and bioenergetics, could offer synergistic benefits in alleviating alcohol-induced mitochondrial damage and liver disease. By addressing multiple pathways simultaneously, these combination therapies may provide more comprehensive protection against ALD progression. Moreover, repurposing existing drugs with known effects on mitochondrial function represents an attractive strategy for quickly translating research findings into clinical applications for ALD treatment.[116,117] This approach could expedite the development of effective therapeutic interventions for

ALD by leveraging the safety profiles and pharmacokinetic properties of existing drugs.

CONCLUSIONS

Understanding the pivotal role of mitochondrial dysfunction in ALD provides a foundation for developing precise interventions and targeted therapies aimed at preserving mitochondrial health and attenuating disease progression. Moving forward, continued research into the molecular mechanisms underlying mitochondrial dysfunction in ALD, coupled with the identification of serum biomarkers to diagnose mitochondrial dysfunction and clinical trials evaluating the efficacy of mitochondrial-targeted therapies, will be crucial in advancing the field and improving outcomes for patients with ALD.

AUTHOR CONTRIBUTIONS

Themis Thoudam and Suthat Liangpunsakul conceptualized the initial draft and composed the original manuscript. Hui Gao, Yanchao Jiang, Nazmul Huda, Zhihong Yang, and Jing Ma revised and edited the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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