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Mitochondrial Dysfunction and Signaling in Chronic Liver Diseases

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Mitochondria regulate hepatic lipid metabolism and oxidative stress. Ultrastructural mitochondrial lesions, altered mitochondrial dynamics, decreased activity of respiratory chain complexes, and impaired ability to synthesize adenosine triphosphate are observed in liver tissues from patients with alcohol-associated and non-associated liver diseases. Increased lipogenesis with decreased fatty acid β-oxidation leads to the accumulation of triglycerides in hepatocytes, which, combined with increased levels of reactive oxygen species, contributes to insulin resistance in patients with steatohepatitis. Moreover, mitochondrial reactive oxygen species mediate metabolic pathway signaling; alterations in these pathways affect development and progression of chronic liver diseases. Mitochondrial stress and lesions promote cell death, liver fibrogenesis, inflammation, and the innate immune responses to viral infections. We review the involvement of mitochondrial processes in development of chronic liver diseases, such as nonalcoholic fatty, alcohol-associated, and drug-associated liver diseases, as well as hepatitis B and C, and discuss how they might be targeted therapeutically.

Keywords: NASH; NAFLD; HCV; HBV; ROS.

Alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD) can progress from benign steatosis to fibrosis, cirrhosis, and hepatocellular carcinoma. Obesity, alcohol, drug use, and chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) are all associated, to different degrees, with increased prevalence of steatosis, characterized by the accumulation of fat droplets within the hepatocytes.[1–7] Steatosis remains benign in most patients, but in some cases leads to hepatocyte necrosis, infiltration of inflammatory cells, and progressive development of fibrosis into cirrhosis.[1,2] The association of steatosis with these other liver lesions is called steatohepatitis.[3–5] Steatohepatitis associates with central obesity, steatosis, diabetes, hyperlipidemia, and insulin resistance (IR).[2,4] In addition to obesity-associated steatohepatitis, there are more-severe forms of fatty liver, associated with alcohol excess,[6–8] some drugs,[9–11] or chronic HBV or HCV infection.[3–6,12]

Mitochondrial dysfunction and oxidative stress have been detected in liver tissues from patients with steatosis and IR, diabetes, non-alcoholic steatohepatitis (NASH), or various stages of alcoholic steatohepatitis (ASH).[1–14] We review mitochondrial functions and oxidative stress, and summarize recent findings on the mechanisms by which mitochondrial dysfunction and altered mitochondrial reactive oxygen species (ROS) affect signaling pathways to contribute to AFLD, NALFD, and hepatitis B and C.

Structure and Dynamics

Mitochondria are organelles evolved from an ancestral bacterium engaged in an endosymbiotic process with an ancestral eukaryote.[15] They keep bacterial vestiges, such as N-formylated proteins, double-stranded circular mitochondrial DNA (mtDNA), and a double membrane—a mitochondrial outer membrane (MOM) delimiting intermembrane space and a mitochondrial inner membrane (MIM) delimiting the mitochondrial matrix. mtDNA encodes 13 polypeptides of mitochondrial respiratory chain (MRC) complexes and adenosine triphosphate (ATP) synthase, 22 transfer RNAs, and 2 ribosomal RNAs required for intra-mitochondrial translation.[16] All other mitochondrial proteins are encoded by nuclear DNA, synthesized in the cytoplasm, and imported into the mitochondria.

Mitochondrial fusion, fission, biogenesis, and mitophagy determine mitochondrial morphology, quality, and abundance, and are tightly controlled in response to metabolic cues and stressors to ensure adaptation of mitochondrial

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Abbreviations used in this paper: **AFLD, alcoholic fatty liver disease; AMPK, adenosine monophosate–activated protein kinase; ASH, alcoholic steatohepatitis; ASK1, mitogen-activated protein kinase kinase kinase 5; ATP, adenosine triphosphate; CoA, coenzyme A; CPT1, carnitine palmitoyl transferase 1; DAMP, damage-associated molecular pattern; FFA, free fatty acid; GSH, glutathione; HBV, hepatitis B virus; HCV, hepatitis C virus; IL, interleukin; IR, insulin resistance; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; mGSH, mitochondrial glutathione; MIM, mitochondrial inner membrane; MnSOD, manganese superoxide dismutase; MOM, mitochondrial outer membrane; MRC, mitochondrial respiratory chain; mtDNA, mitochondrial DNA; mtUPR, mitochondrial unfolded protein response; NAD, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; NAFLD, nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NRF, nuclear respiratory factor; PGC-1α, peroxisome proliferator activated receptor γ–coactivator 1α; PPARα, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; SREBP-1c, sterol regulatory element binding transcription factor 1 variant 1-c; TNF, tumor necrosis factor; VLDL, very-low-density lipoprotein.**

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function to cellular energetic and metabolic demands. Fusion of the MOM is mediated by mitofusins 1 and 2, whereas the fusion of MIM requires optic atrophy protein 1.[17] Mitochondrial fission requires dynamin-related protein 1, which is recruited by the mitochondrial fission 1 protein.[18]

Mitochondrial biogenesis maintains mitochondrial mass to restore energy homeostasis during energy deprivation or following mitochondrial insults. Mitochondrial biogenesis is regulated by peroxisome proliferator–activated receptor gamma coactivator 1α (PPARGC1A or PGC-1α) and nuclear respiratory factor 1 (NRF1), which control expression of mtDNA and nuclear DNA genes encoding subunits of the MRC complexes and mtDNA replication and transcription, respectively.[19–21]

Defective mitochondria are cleared via PTEN-induced putative kinase 1 and parkin-mediated mitophagy to control mitochondrial quality.[22,23] The mitochondrial unfolded protein response (mtUPR) maintains mitochondrial homeostasis, controls the stochiometric balance between proteins encoded by the nuclear and mitochondrial genomes, ensures mitochondrial quality and proteostasis, and senses mitochondrial protein misfolding.[24,25]

Mitochondria are required for fat metabolism and energy production, the urea cycle, and metabolism of amino acids and iron,[1,2,14] regulating signaling pathways that mediate these processes.[26–30] Mitochondria regulate the innate immune response to control inflammation and associated diseases.[20–23] Alterations in these processes can contribute to development and progression of liver diseases.[1,21,23,26,28–38]

Formation of Reactive Oxygen Species and Mitochondrial Antioxidant Defense

Mitochondria are the major site of ROS formation in the cell[5,39] (Figure 1*A*). Although most of the electrons donated to the MRC migrate down to cytochrome *c* oxidase, where they react with protons and oxygen to form water, some of these electrons react directly with oxygen to form the superoxide anion ($O_2^{\cdot-}$) radical, leading to formation of hydrogen peroxide (H_2O_2).

Manganese superoxide dismutase allows the spontaneous dismutation of the $O_2^{\cdot-}$ into oxygen and H_2O_2, which is then detoxified into water by mitochondrial glutathione (GSH) peroxidase and peroxiredoxins.[39,40] Alternatively, H_2O_2 reacts with iron to form the highly reactive hydroxyl radical[39–41] and active myeloperoxidase forms the hypochloride radical[42] (Figure 1*A*).

Although there has been debate over the presence of nitric oxide synthase within mitochondria, the freely diffusible nitric oxide formed elsewhere can cross mitochondrial membranes to react with superoxide and form peroxynitrite within mitochondria.[31,43] Peroxynitrite causes formation of 3-nitrotyrosine residues on several proteins, including complex I and V subunits.[31,44] Peroxiredoxins and selenium-containing glutathione peroxidase catalytically detoxify peroxynitrite.[45] These oxygen and nitrogen radicals damage mtDNA, proteins, and lipids, increasing further ROS production in a vicious cycle.

Signal Transduction by Mitochondrial Reactive Oxygen Species

Beside their damaging effects, mitochondrial ROS are also signal-transducing molecules under physiological and pathological conditions, depending on the intensity and duration of oxidative stress.[27,29] Low-intensity production of ROS is important in metabolic adaptation, moderate ROS release may be involved in regulating inflammatory mediators, and high levels of ROS activate pathways, such as apoptosis or autophagy. In each case, different H_2O_2-sensitive pathways are mobilized.[27–29]

Mitochondria-derived ROS activate adenosine monophosate–activated protein kinase (AMPK)[26,28] and mitogen-activated protein kinases (MAPKs), such as c-Jun N-terminal kinase (JNK).[29] Their substrate phosphorylation has direct consequences on diverse metabolic pathways, regulation of gene expression by transcription factors, and direct activation or inhibition of specific target proteins, such as protein tyrosine phosphatases and protein kinases. AMPK and MAPK signaling pathways are activated in response to different stresses, including alterations in nutrients, cytokines, growth factors, drugs, and toxins—these signaling pathways have important roles in development of liver diseases and injuries, such as NAFLD, ALD, viral hepatitis, fibrosis, inflammation, carcinogenesis, and drug-induced hepatotoxicity.[26,28,29]

Role of Mitochondria in Fatty Acid Metabolism and Energy Supply

The β-oxidation of fatty acids into acetyl-coenzyme A (CoA), and its oxidation by the Krebs cycle, lead to reduced forms of reduced nicotinamide adenine dinucleotide (NADH) and reduced flavine-adenine dinucleotide, which transfer their electrons to the MRC[46] (Figure 1*B*). This transfer of electrons is coupled to the extrusion of protons from the mitochondrial matrix to the intermembrane space, creating a large electrochemical gradient across the MIM.[9] The energy released, when these protons re-enter into the matrix through ATP synthase, drives ATP synthesis.[1,3,13]

AMPK stimulates glucose and fatty acid oxidation, and activates PGC-1α.[26,28] PGC-1α interacts with peroxisome proliferator–activated receptor α (PPARα) to induce the expression of several fatty acid-metabolizing enzymes, including carnitine palmitoyltransferase 1 (CPT1) and acyl-CoA dehydrogenases, consequently increasing mitochondrial β-oxidation of fatty acid.[9,46] PGC-1α also induces the expression of, and bind to NRF1 to increase the expression of TFAM.[4,14,47] NRF1 and TFAM regulate the transcription and the replication of mtDNA, whereas NRF1 regulates expression of nuclear DNA-encoded MRC proteins. PGC-1α thereby increases the mitochondrial mass, as well as the mitochondrial oxidative phosphorylation capacities.[20]

Liver free fatty acids (FFAs) arise from plasma FFAs released by adipose tissue, and from intestine chylomicrons, or are synthesized de novo within the hepatocytes.[13,14] These FFAs either enter mitochondria to undergo β-oxidation or are esterified and stored as