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Mitochondrial Quality Control in Metabolic Dysfunction-Associated Steatotic Liver Disease: Mechanisms and Pathophysiological Implications

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Abstract. Metabolic dysfunction-associated steatotic liver disease (MASLD), currently recognized as the leading chronic liver disorder worldwide, encompasses a broad clinical and pathological continuum, extending from isolated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Although considerable progress has been made in characterizing the disease's pathophysiology, the molecular and cellular processes governing its progression have yet to be fully clarified. Increasing evidence implicates mitochondrial dysfunction (MD) as a major contributor to MASLD development and progression, reflecting the fundamental involvement of mitochondria in hepatic bioenergetics, lipid metabolism, redox homeostasis, and the regulation of cellular stress responses.

Of particular importance, impairment of mitochondrial quality control (MQC) compromises the maintenance of mitochondrial integrity and functionality. Alterations in mitochondrial biogenesis, organelle dynamics, mitophagy, and the mitochondrial unfolded protein response (mt-UPR) may collectively exacerbate metabolic disturbances, promote hepatocellular injury, and contribute to the progression of liver disease.

Objective: To explore the role of MQC mechanisms in the pathogenesis and progression of MASLD, with particular emphasis on mitochondrial biogenesis, dynamics, mitophagy, and the mt-UPR.

Materials and methods. A narrative literature review was conducted using publications retrieved from PubMed/MEDLINE, Scopus, and Web of Science. The review focused on the role of MQC mechanisms, including mitochondrial biogenesis, dynamics, mitophagy, and the mt-UPR, in the pathogenesis and progression of MASLD. Particular attention was given to studies investigating the interactions between MQC pathways, mitochondrial homeostasis, hepatocellular stress, and disease progression.

Results. Mitochondrial quality control (MQC) comprises a coordinated network of cellular mechanisms responsible for preserving mitochondrial integrity, detecting organelle damage, and maintaining functional homeostasis under physiological and pathological conditions [1]. Disruption of these regulatory pathways, encompassing the mitochondrial integrated stress response, mitochondrial biogenesis, mitochondrial

dynamics, mitophagy, and intercellular mitochondrial transfer, may facilitate the onset and progression of MASLD. The following sections examine the contribution of each of these processes to disease pathophysiology.

Mitochondrial Integrated Stress Response

The mitochondrial integrated stress response (mt-ISR) represents an adaptive signaling network that coordinates transcriptional and metabolic responses to mitochondrial dysfunction. Its activation may be induced by impaired oxidative phosphorylation (OXPHOS), mitochondrial membrane depolarization, excessive reactive oxygen species (ROS) generation, amino acid deprivation, and the accumulation of misfolded proteins [2]. In MASH, impaired mitochondrial respiratory activity is associated with diminished adenosine triphosphate (ATP) synthesis and enhanced oxidative stress, contributing to the disruption of mitochondrial homeostasis [3].

Under persistent mitochondrial stress, the accumulation of unfolded and misfolded proteins within the mitochondrial matrix may activate the mitochondrial mt-UPR, a key component of the mitochondrial stress-adaptive machinery. This response involves the enhanced expression of mitochondrial proteases and molecular chaperones, facilitating the removal of damaged proteins and the restoration of protein homeostasis. Mt-UPR activation is also associated with increased production of mitokines, particularly fibroblast growth factor 21 (FGF21), which mediates interorgan metabolic signaling [4]. Alterations in FGF21 expression and signaling have been associated with MASLD development and progression, suggesting a potential link between mitochondrial stress responses and hepatic metabolic dysfunction [5].

Impaired Mitochondrial Biogenesis and Dynamics

Dysregulation of mitochondrial biogenesis and dynamics is increasingly recognized as an important feature of MASLD progression, particularly during the transition from simple steatosis to MASH. These alterations are accompanied by ultrastructural abnormalities, including mitochondrial enlargement, matrix swelling, disruption of cristae architecture, and paracrystalline inclusions. In patients with MASLD, impaired mitochondrial biogenesis and oxidative capacity have been associated with reduced hepatic expression of key regulatory proteins, including peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), nuclear respiratory factor 1, and mitochondrial transcription factor A, as well as alterations in electron transport chain components [6].

PGC-1α is a central regulator of mitochondrial biogenesis and oxidative metabolism. Its reduced expression has been linked to impaired AMP-activated protein kinase, sirtuin 1, endothelial nitric oxide synthase, and mitogen-activated protein kinase signaling pathways in the context of fatty acid overload. Disruption of these regulatory mechanisms may compromise mitochondrial renewal and energy production. Consistently, steatotic mouse livers exhibit reduced mitochondrial abundance and hepatic ATP content, supporting the association between impaired mitochondrial biogenesis and hepatic energy deficiency [7].

Mitochondrial dynamics, involving the coordinated processes of fusion and fission, are essential for maintaining organelle integrity and functional adaptation to

metabolic stress. Reduced expression of mitofusin 1, mitofusin 2 (MFN2), and optic atrophy 1 (OPA1), which regulate mitochondrial fusion, has been associated with altered mitochondrial morphology and impaired bioenergetic function. High-fat diet exposure further suppresses the expression of these proteins. Notably, hepatocyte-specific MFN2 deficiency aggravates metabolic disturbances, whereas restoration of MFN2 expression attenuates hepatic lipid accumulation and inflammation in experimental models [8]. Furthermore, hyperglycemia may interfere with OPA1-mediated mitochondrial fusion, promoting mitochondrial fragmentation and functional impairment [9]. Collectively, these findings indicate that defective mitochondrial biogenesis and disturbed fusion-fission balance may contribute to the loss of mitochondrial homeostasis and MASLD progression.

Mitophagy Dysregulation

Mitophagy is a selective form of autophagy that eliminates dysfunctional or damaged mitochondria through lysosomal degradation, thereby preserving mitochondrial integrity and cellular homeostasis. This process is essential for maintaining a functional mitochondrial pool, particularly under conditions of metabolic stress.

However, an imbalance in mitophagic activity may also be detrimental: insufficient mitochondrial clearance promotes the accumulation of damaged organelles, whereas excessive mitophagy may lead to mitochondrial depletion, impaired cellular bioenergetics, and increased susceptibility to cell death [10].

The phosphatase and tensin homolog-induced kinase 1 (PINK1)/Parkin signaling pathway represents a major mechanism underlying mitochondrial damage recognition and selective mitochondrial degradation. Its dysregulation has been implicated in MASLD pathogenesis. Experimental models of diet-induced MASLD demonstrate reduced PINK1 and Parkin expression, accompanied by impaired mitophagic activity and increased hepatic injury. Furthermore, increased macrophage-stimulating 1 expression has been associated with disruption of Parkin-mediated mitophagy. Reduced Parkin expression has also been observed during early stages of MASLD and linked to more rapid disease progression, suggesting that impaired mitochondrial clearance may contribute to disease development even before advanced liver injury becomes apparent [11].

Failure to remove dysfunctional mitochondria may result in their progressive accumulation, aggravating oxidative stress and compromising OXPHOS and ATP production. These alterations may further disturb hepatic lipid metabolism, favor intracellular lipid accumulation, and contribute to hepatocellular injury and MASLD progression [12]. Thus, maintaining an appropriate balance of mitophagic activity is essential for mitochondrial homeostasis and metabolic adaptation in the liver.

Impaired Intercellular Mitochondrial Transfer

Intercellular mitochondrial transfer (MT) represents an additional mechanism of cellular communication and metabolic adaptation through which mitochondria are exchanged between neighboring or distant cell populations. This process may contribute to mitochondrial quality control by supporting the functional recovery of

recipient cells and maintaining tissue metabolic homeostasis. Emerging evidence suggests that hepatocytes can participate in intercellular mitochondrial exchange, while disruption of this process may adversely affect hepatic metabolic function.

Experimental evidence from an in vitro multicellular co-culture model indicates that cadmium exposure impairs mitochondrial transfer between hepatocytes by disrupting the microtubule network and reducing the formation of tunneling nanotubes, which serve as conduits for organelle exchange. These alterations were accompanied by increased intracellular lipid accumulation, suggesting a potential link between impaired mitochondrial transfer and disturbed hepatic lipid homeostasis [13].

Furthermore, alterations in intercellular MT have been associated with obesity and MASLD and may contribute to impaired energy regulation, glucose intolerance, and abnormal adiposity [14]. Nevertheless, the precise molecular pathways governing mitochondrial exchange in the liver, as well as the relative contribution of this process to MASLD development and progression, remain poorly understood. Further studies are required to establish its physiological significance and potential therapeutic relevance.

Conclusions. MQC is essential for maintaining hepatic mitochondrial integrity and metabolic homeostasis in MASLD. Disruption of mitochondrial stress responses, biogenesis, dynamics, and mitophagy, together with alterations in intercellular mitochondrial transfer, may contribute to mitochondrial dysfunction, impaired energy metabolism, oxidative stress, and hepatocellular injury. These interconnected mechanisms may facilitate the transition from simple steatosis to MASH and subsequent disease progression. Further investigation of MQC pathways may provide insights into MASLD pathophysiology and identify potential targets for mitochondria-directed therapeutic interventions.

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