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Review

COVID-19 induced liver injury from a new perspective: Mitochondria

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ABSTRACT

Liver damage is a common sequela of COVID-19 (coronavirus disease 2019), worsening the clinical outcomes. However, the underlying mechanism of COVID-induced liver injury (CiLI) is still not determined. Given the crucial role of mitochondria in hepatocyte metabolism and the emerging evidence denoting SARS-CoV-2 can damage human cell mitochondria, in this mini-review, we hypothesized that CiLI happens following hepatocytes' mitochondrial dysfunction. To this end, we evaluated the histologic, pathophysiologic, transcriptomic, and clinical features of CiLI from the mitochondria' eye view. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, can damage hepatocytes through direct cytopathic effects or indirectly after the profound inflammatory response. Upon entering the hepatocytes, the RNA and RNA transcripts of SARS-CoV-2 engages the mitochondria. This interaction can disrupt the mitochondrial electron transport chain. In other words, SARS-CoV-2 hijacks the hepatocytes' mitochondria to support its replication. In addition, this process can lead to an improper immune response against SARS-CoV-2. Besides, this review outlines how mitochondrial dysfunction can serve as a prelude to the COVID-associated cytokine storm. Thereafter, we indicate how the nexus between COVID-19 and mitochondria can fill the gap linking CiLI and its risk factors, including old age, male sex, and comorbidities. In conclusion, this concept stresses the importance of mitochondrial metabolism in hepatocyte damage in the context of COVID-19. It notes that boosting mitochondria biogenesis can possibly serve as a prophylactic and therapeutic approach for CiLI. Further studies can reveal this notion.

1. Introduction

The ongoing coronavirus disease 2019 (COVID-19) is a major health threat worldwide. This viral disease happens upon colonization and proliferation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the respiratory tract. Thereafter, COVID-19 enters the inflammatory phase, in which dysregulated systemic inflammatory response (termed as cytokine storm) can lead to multiorgan failure (Griffin et al., 2021). After the lungs, the liver is the second most affected organ in the context of COVID-19 (Wanner et al., 2022). Abnormally high levels of liver enzymes, a marker of hepatocyte damage and death, are commonly observed in patients with COVID-19, resulting in hospitalization, mechanical ventilation, and death (Lei et al., 2020). COVID-induced liver injury (CiLI) is defined as any liver damage occurring during the disease course regardless of pre-existing liver disease (Gracia-Ramos et al., 2021). In different studies, the incidence of CiLI varied from 14 to 53 % of infected cases (Chen et al., 2021). SARS-CoV-2 can damage hepatic tissue through direct effects on hepatocytes or indirectly through systemic inflammation (see Section 2). The histologic manifestations of CiLI are widely distinct, including hepatocyte steatosis, polyploidization, and portal and lobular inflammation, which can lead to hepatic sinus congestion and microthrombosis (Wang et al., 2020). It has been demonstrated that CiLI can significantly increase the risk of COVID severity and mortality (Lei et al., 2020). This is because liver is a major organ in the human body and regulates the metabolic flexibility of the whole body in response to fluctuations in energy demands and supplies (Morio et al., 2021). Despite significant findings, it is still not clarified how SARS-CoV-2 injures hepatic cells. Considering mitochondria are the master regulators of cellular metabolism (Spinelli and Haigis, 2018), and given that SARS-CoV-2 can damage human cell mitochondria (De la Cruz-Enríquez et al., 2021), we hypothesized that COVID-induced liver damage manifests mitochondrial dysfunction.

Mitochondria are the major organelles responsible for energy production for cell survival and function, so named the human cells' powerhouses. Besides, mitochondria regulate numerous signaling pathways,

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Nomenclature

Abbreviations

ACE2	Angiotensin-converting enzyme 2
AMPK	Adenosine monophosphate-activated protein kinase
AST	Aspartate aminotransferase
AT1R	Angiotensin II type 1 receptor
ATP	Adenosine triphosphate
CiLI	COVID-induced liver injury
COVID-19	Coronavirus disease 2019
DaG	Diammonium glycyrrhizinate
DAMPs	Damage-associated molecular patterns
dsRNA	Double-stranded RNA
GPX4	Glutathione peroxidase-4
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIF-1	Hypoxia-inducible factor 1
IFN	Interferon-1
IL	Interleukin
MAVS	Mitochondrial antiviral signaling
MgIG	Magnesium isoglycyrrhizinate
MRSA	Methicillin-resistant staphylococcus aureus
MSSA	Methicillin-sensitive staphylococcus aureus
mTOR	Mammalian target of rapamycin
NADH	Nicotinamide adenine dinucleotide
NASH	Non-alcoholic steatohepatitis
NSP	Non-structural protein
ORF	Open reading frame
pDC	Plasmacytoid dendritic cells
PGC-1α	Proliferator-activated receptor gamma coactivator 1-alpha
RAS	Renin-angiotensin system
ROS	Reactive oxygen species
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TCA	Tricarboxylic acid
TLR	Toll-like receptor
TMPRSS2	Transmembrane serine protease 2
TNF-α	Tumor necrosis factor-α
USP30	Ubiquitin-specific peptidase 30

including apoptosis and calcium homeostasis (Murphy et al., 2016). In addition, functional mitochondria rapidly sense and respond to intrinsic (e.g., DNA mutation, nutrient deprivation) and extrinsic stressors (e.g., toxins and infectious agents) in different ways—including fusion/fission, intracellular movements, changing in their mass and metabolism, and remodeling their cristae—to improve the cellular tolerance and reaction to the imposed stressor (Eisner et al., 2018). In hepatocytes, mitochondria have specific roles in regulating metabolism (e.g., gluconeogenesis, lipogenesis, ureagenesis, and ketogenesis) and coordinating innate immune response (Morio et al., 2021). A large body of evidence noted that mitochondria are the targets for the common risk factors of liver diseases, including alcohol (Abdallah and Singal, 2020), hepatitis B virus (HBV) (Hossain et al., 2020), hepatitis C virus (HCV) (Kim et al., 2014), and antibiotics (e.g., ciprofloxacin and amoxicillin/clavulanate) (Oyebode et al., 2019). In addition, it has been demonstrated that mitochondrial dysfunction is associated with chronic liver diseases in the context of obesity, diabetes mellitus, and non-alcoholic steatohepatitis (NASH) (Morio et al., 2021).

With these understandings in mind, we sought to find if hepatic cells' mitochondria are the main targets of SARS-CoV-2. This review summarizes the current knowledge about the CiLI from the mitochondria' eye view. The following sections describe the mechanisms underlying the CiLI (Sections 2 and 3) and its risk factors (Section 4). This concept can open an avenue to reduce liver damage incidence and severity in the context of COVID-19 by applying tactics to improve mitochondria biogenesis, as outlined in Section 5.

2. Mechanisms underlying COVID-induced liver injury: Current understandings

Patients with COVID-19 have different degrees of liver damage, but the underlying mechanism remains unclear. Liver damage in the context of COVID-19 may occur through direct cytopathic effects of SARS-CoV-2, or secondary to excessive systemic inflammatory response (Zhang et al., 2022). This section outlines these two mechanisms. Section 3 presents how mitochondria might involve in these processes.

2.1. Direct effects

SARS-CoV-2 may access liver tissue through blood circulation or retrograde migration via the portal venous system (Zhang et al., 2022). The latter is more probable because the infectious virus is generally at low viral loads in the systemic circulation of patients with COVID-19 (Andersson et al., 2020). Upon access to liver tissue, the viruses bind the angiotensin-converting enzyme 2 (ACE2) receptor on hepatocytes by their surface spike proteins (so-called S proteins). The SARS-CoV-2 attachment to the host cells is 10–20 times more potent than previous coronavirus variants (Wrapp et al., 2020). After binding, the host transmembrane serine protease 2 (TMPRSS2) primes ACE2 and facilitates virus entry into the cell. Once entering the hepatocyte, the virus becomes uncoated and releases its RNA into the cytosol to run intracellular proliferation by applying the host cells' facilities (Nardo et al., 2021). In this process, the virus's RNA is translated into structural (e.g., M protein) and nonstructural proteins (NSP1 to 16). In parallel, the viral genome is replicated to generate more RNA molecules. The newly synthesized viral genome is enveloped by the proteins, and the new viruses are released from host cells via exocytosis (Nardo et al., 2021). In this context, SARS-Cov-2 can damage hepatocytes through different mechanisms: (1) hepatocytes are metabolically active cells, a feature making them sensitive to hypoxia. COVID-19 lead to different degrees of hypoxemia, secondary to pulmonary involvement. In addition, SARS-CoV-2 can directly damage hepatic sinusoidal endothelial cells, leading more liver tissue hypoxia. Under hypoxic conditions, reactive oxygen species (ROSs) accumulate in hepatocytes, propelling them toward cell death (Bhogal et al., 2011). Furthermore, with a decrease in oxygen pressure, the expression of ACE2 receptor on hepatocytes gradually increases, which can facilitate the entry of viruses into hepatocytes (Paizis et al., 2005); (2) claudin proteins on cholangiocytes maintain the barrier function of bile ductal epithelium and keep the bile acid flow in the intercellular space. It has been demonstrated that SARS-CoV-2 can downregulate the claudin expression in cholangiocytes, leading bile acid reflux and hepatocytes damages (Zhao et al., 2020). However, further evaluation of COVID patients' liver tissues has opened new dimensions of CiLI, the mitochondria. Section 3 describes how mitochondria can be involved in the CiLI process.

2.2. Systemic inflammation

Besides direct effects on tissue, SARS-CoV-2 can induce a profound systemic inflammation (a.k.a *cytokine storm*) that damages vital organs, including the liver (Taneva et al., 2021). In this process, SARS-CoV-2 dysregulates the renin-angiotensin system (RAS) signaling pathway and promotes angiotensin toward the angiotensin II type 1 receptor (AT1R) axis, leading to a robust release of pro-inflammatory cytokines, such as interferon-1 (IFN-1), interleukine-6 (IL-6), prostaglandins, and tumor necrosis factor-α (TNF-α), from immune cells (Ali et al., 2021).

The RAS imbalance into the pro-inflammatory state has pro-oxidative, pro-fibrotic, and pro-apoptotic consequences on human tissues (El-Arif et al., 2022). In a study on patients with COVID-19, Effenberger et al. found that aspartate aminotransferase (AST), as a marker of hepatocytes damage and death, was significantly elevated in patients with a higher IL-6, ferritin, and c-reactive protein (CRP) (Effenberger et al., 2021). This finding demonstrates that although pro-inflammatory cytokines are required for a proper anti-viral immune activation, their release must be carefully controlled due to the detrimental effects of profound cytokine production on normal tissues. In addition, acute and exaggerated immune activation against SARS-CoV-2 can deplete the energy repositories of immune cells, which reduce their sustained immunosurveillance against the pathogen (Taghizadeh-Hesary and Akbari, 2020). Section 3.2 discusses how mitochondria can be involved in the COVID 19-induced massive cytokine release.

3. Mechanisms underlying COVID-induced liver injury: How mitochondria are involved

3.1. Direct effects

Liver autopsy specimens of individuals with COVID-19 have revealed three crucial findings: binuclear hepatocytes (a.k.a polyploidization), steatosis, and SARS-CoV-2 particles besides the swollen mitochondria (Wang et al., 2020). The latter finding might address that hepatocytes' mitochondria are the targets of SARS-CoV-2. Further studies endorsed this notion. In a study on Huh7 cells, Shang et al. found the double-stranded RNA (dsRNA) of SARS-CoV-2 in the mitochondria matrix. The investigators pointed out that the viral RNA can enter the mitochondria via the Tom20 receptor to facilitate replication. This interaction can disrupt mitochondrial membrane depolarization and increase mitochondrial membrane permeability resulting in mitochondrial ROS release to the cytosol and host cell apoptosis (Shang et al., 2021). This process has also been demonstrated in immune cells (Ganji and Reddy, 2020). In a normal state, mitochondria need to constantly run fission and fusion to maintain cellular homeostasis. However, in the case of COVID-19, the fission process is utterly inhibited, causing mitochondrial elongation and providing a receptive intracellular environment for viral replication (Holder and Reddy, 2021). The release of SARS-CoV-2′s RNA to the cytosol can disrupt mitochondrial function in several other ways (Fig. 1):

(1) the structural M protein of SARS-CoV-2 can increase mitochondrial outer membrane permeabilization, leading to host cell apoptosis through the release of caspases (Srinivasan et al., (2021)); (2) the NSP8 interferes with mitochondrial translation machinery, leading to mitochondrial dysfunction (Gordon et al., 2020); (3) the NSP10 reduces the NADH-cytochrome oxidase II activity, leading mitochondrial dysfunction through mitochondrial membrane depolarization (Srinivasan et al., 2021); (4) the open reading frame 3a (ORF3a) encoded protein interacts with ubiquitin-specific peptidase 30 (USP30) and disrupt the mitochondrial homeostasis by inhibiting the mitophagy of infected mitochondria (Shang et al., 2021); (5) the ORF9b impedes the IFN-mediated antiviral response by inhibiting mitochondrial antiviral signaling (MAVS) protein (Shi et al., 2014); (6) the ORF8a can lead to oxidative

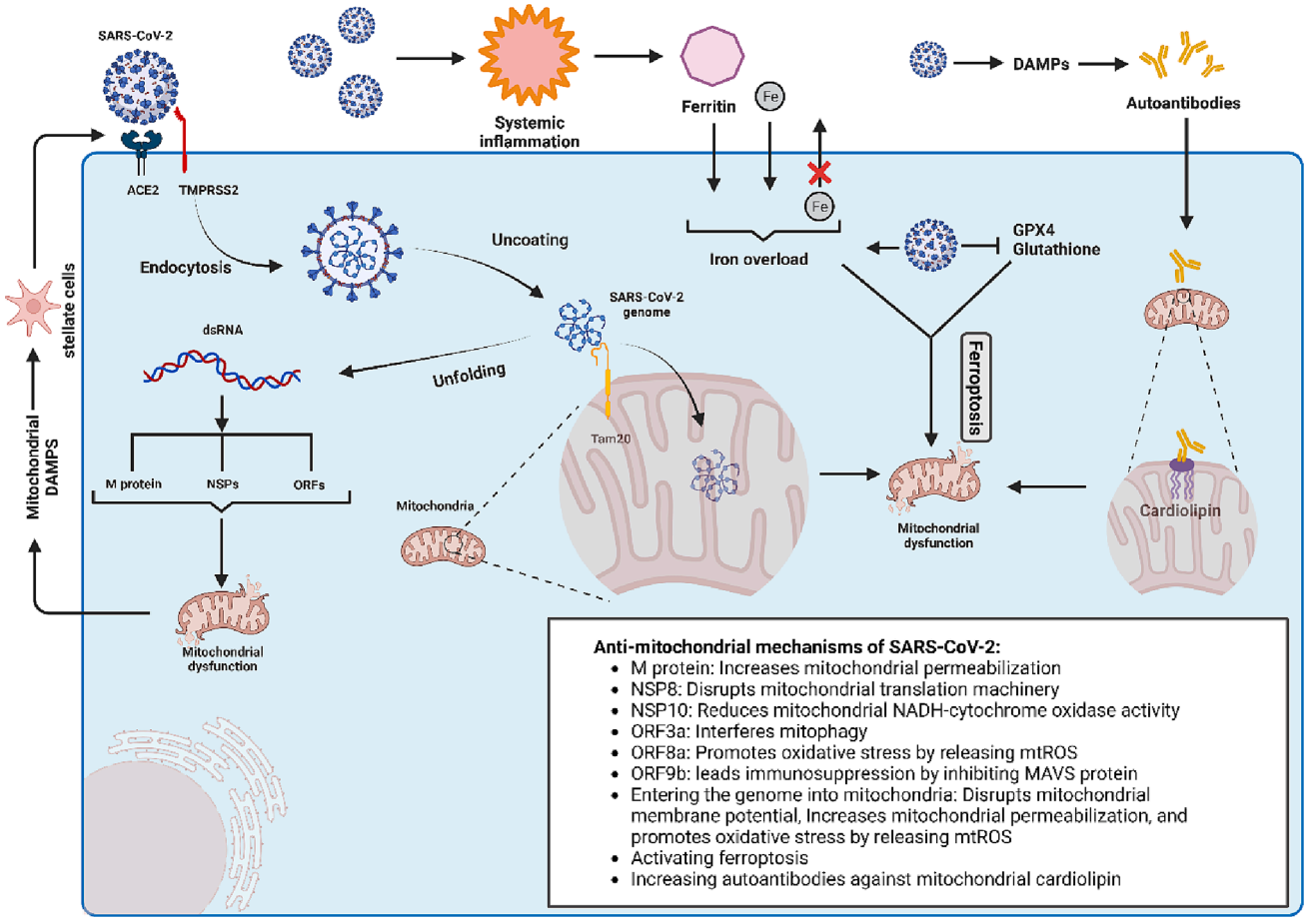

Fig. 1. Schematic view of COVID-induced liver injury from the perspective of mitochondria. ACE2 indicates angiotensin-converting enzyme 2; DAMPs, damage-associated molecular patterns; dsRNA, double-stranded RNA; Fe, iron; GPX4, glutathione peroxidase-4; MAVS, mitochondrial antiviral signaling; mtROS, mitochondrial reactive oxygen species; NADH, nicotinamide adenine dinucleotide; NSP, non-structural protein; ORF, open reading frame; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2.

stress through an increase in ROS production (Srinivasan et al., 2021).

Recent evidence has pointed out another mechanism of CiLI, ferroptosis. It is an iron-dependent programmed cell death characterized by iron overload and lipid peroxidation through the Fenton reaction. During ferroptosis, mitochondria are mainly targeted by iron-caused oxidative stress, representing mitochondrial shrinkage, cristae deformation, and increased mitochondrial membrane potential (Dixon et al., 2012). It has been demonstrated that SARS-CoV-2 can lead to ferroptosis through several mechanisms, including (1) intracellular iron overload through transferrin receptor-1 (Chen et al., 2022; Suriawinata and Mehta, 2022); (2) suppression of GPX4 (glutathione peroxidase-4) expression that is a negative regulator of ferroptosis (Wang et al., 2021); (3) intracellular iron overload by increasing the serum ferritin (as an acute phase reactant) and running ferritniophagy (Mancias et al., 2014); (4) decrease in cellular glutathione level that inhibits lipid peroxidation (Bartolini et al., 2021); and (5) inhibiting the cellular efflux of iron through ferroportin by activating hepcidin (Banchini et al., 2020). Ferroptosis is an immunogenic process (Sun et al., 2020). Therefore, COVID-induced ferroptosis can aggravate CiLI. In a histopathological examination of patients with COVID-19, Del Nonno et al. demonstrated that iron overload is the possible mechanism of CiLI (Del Nonno et al., 2021). In a clinical study, Szabo et al. demonstrated that higher baseline hepcidin and ferritin levels were associated with a higher multi-organ dysfunction rate in patients with COVID-19 (Szabo et al., 2022). The negative impacts of SARS-CoV-2 on mitochondria and the resultant reduced cellular glutathione levels can impair redox homeostasis and further propose the mitochondria to systemic inflammation and ferroptosis-induced oxidative damage (Bartolini et al., 2021; Grossini et al., 2021).

COVID-19 can instantly increase liver fibrogenesis (Kolesova et al., 2021). This event can be justified by the negative impacts of SARS-CoV-2 on hepatocyte mitochondria. It has been demonstrated that releasing mitochondria-derived damage-associated molecular patterns (DAMPs) from damaged mitochondria can drive liver fibrosis by activating hepatic stellate cells (An et al., 2020). Under the condition of liver fibrosis, the expression of ACE2 increases (Li et al., 2022). This effect can further aggravate the CiLI. COVID-induced oxidative stress can lead to polyploidization of hepatocytes (Wang et al., 2020), which has also been reported in the context of oxidative stress due to mitochondrial dysfunction in patients with NASH (Gentric et al., 2015). Another histopathological manifestation of CiLI is micro/macrovesicular steatosis, which is a hallmark of mitochondria dysfunction in patients with NASH (Xu et al., 2021). Therefore, mitochondria dysfunction can justify the histopathological appearance of damaged hepatocytes in the context of COVID-19.

Besides the histopathological findings, the gene expression signature of SARS-CoV 2-infected hepatocytes addresses the mitochondrial dysfunction. In a bioinformatic analysis of forty-two liver autopsy specimens, Wanner et al. found that SARS-CoV-2 can lead to a down-regulation of several genes in hepatocytes, most of which are responsible for regulating mitochondrial electron transport chain and cellular respiration (Wanner et al., 2022). These findings reflect that mitochondrial engagement by SARS-CoV-2 can dysregulate mitochondrial function, leading to hepatocyte dysfunction and death.

3.2. Indirect effects

3.2.1. Systemic inflammation

As alluded to above, SARS-CoV-2 dysregulates the immune cells to produce massive pro-inflammatory cytokines. Among the immune cells, plasmacytoid dendritic cells (pDCs) are of special interest as they are the sentinels in the innate immune response to SARS-CoV-2. In addition, pDCs are the main source of IFN-1 as a pro-inflammatory cytokine in the COVID-induced cytokine storm (Van der Sluis et al., 2022). The pDCs detect the viruses by their superficial toll-like receptor 7 (TLR7). Upon binding to SARS-CoV-2, TLR7 mediates the production of IFN-1 (Van der Sluis et al., 2022). The regulated release of IFN-1 is dependent on the *endo*-lysosomal PH; in order that an increase in the *endo*-lysosomal PH would enhance the IFN production (Rebbapragada et al., 2016). It has been demonstrated that regulating the *endo*-lysosomal PH is adenosine triphosphate (ATP)-dependent process; in order that a decrease in cellular ATP can increase the *endo*-lysosomal PH (Rebbapragada et al., 2016). Therefore, COVID-induced cytokine storm might happen upon mitochondrial damage in the following two ways: (a) SARS-CoV-2 damages the pDCs' mitochondria directly (see Section 3.1 or through systemic inflammation (see below); mitochondrial dysfunction results in a reduction of the pDCs' ATP content; reduce in ATP would increase the *endo*-lysosomal PH of pDCs; IFN-1 production disproportionately increases in a high *endo*-lysosomal PH, which would result in COVID's *cytokine storm*. (b) SARS-CoV-2 can trigger systemic inflammation by damaging the mitochondria and releasing the mitochondrial DNA (Singh et al., 2020). This effect is mediated through several signaling pathways, including TLR and cGAS-cGAMP-STING pathways (Mahmoodpoor et al., 2022). It has been demonstrated that human alveolar epithelial cells with dysfunctional mitochondria release large amounts of cytokines following SARS-CoV-2 infection. This event aggravates systemic inflammation-induced oxidative stress, which impairs the coagulation cascade and contributes to microbiota dysbiosis. The resultant vicious cycle aggravates clotting events and systemic inflammation (Saleh et al., 2020).

In patients with COVID-19, angiotensin II leads to intracellular oxidative stress through AT1R-dependent induction of NADPH oxidase, which can damage intracellular organelles-including mitochondria (El-Arif et al., 2022). Subsequent to the impaired mitochondrial membrane potential, mitochondrial K-ATP channels will open that further aggravating the oxidative stress by releasing the mitochondrial ROS (El-Arif et al., 2022). This process can propel the status to a vicious cycle; in order that the oxidative stress can damage the pDCs' mitochondria, which in turn enhances the TLR7-dependent IFN-1 production. This section illustrated how mitochondrion can serve as either victim or murderer of COVID-associated cytokine storm.

3.2.2. Autoimmunity

Section 3.1 noted that COVID-19 can damage hepatocytes' mitochondria through ferroptosis. In this process, iron-activated ROSs oxidize cellular lipidic structures, including mitochondrial membrane phospholipids. Notably, Wiernicki et al. demonstrated that cardiolipin (a phospholipid in the mitochondrial inner membrane) is resistant to ferroptosis (Wiernicki et al., 2020). It is a key phospholipid playing crucial roles in mitochondrial processes, including respiration and energy production (Dudek, 2017). It has been shown that COVID-19 can damage mitochondrial cardiolipin by damaging human cells and releasing DAMPs, such as extracellular DNA. Bertin et al. demonstrated that in response to extracellular DNA, the IgG autoantibodies directly attack mitochondrial cardiolipins (Bertin et al., 2022).

4. Risk factors of COVID-induced liver injury and how mitochondria play a role

The available studies have determined different risk factors of liver damage in patients with COVID-19. However, the underlying mechanism(s) still needs to be determined. This section outlines how mitochondrial dysfunction can link the proposed risk factors and CiLI.

4.1. Old age

It has been evidenced that old age is a significant risk factor for CiLI in terms of incidence (Zhang et al., (2021)) and severity (Chen et al., 2021). However, the underlying reasons are still unknown. The association between aging and mitochondrial dysfunction is well established. Aging is typified by a progressive decline in mitochondrial activity. This can be manifested as impaired redox homeostasis, fission/fusion,

mitophagy, and apoptosis (Lima et al., 2022). Therefore, one may link the increased risk of CiLI in older ages because of impaired mitochondrial function.

4.2. Gender

The literature regarding gender as a risk factor for CiLI is inconsistent. Shen et al. demonstrated that the male sex is an independent RF of CiLI. (Shen et al., (2021)) This finding was confirmed in a large cohort by Chen et al. from Huazhong University (Chen et al., 2021). On the other hand, Zhang et al. reported more CiLI in female patients (Zhang et al., 2021). The latter study's findings might enface bias due to not excluding patients with a history of chronic liver diseases (e.g., viral hepatitis, alcoholic liver disease, liver cancer, and autoimmune liver disease), a crucial issue which was considered by Shen et al. With this preface, we considered male sex, as a risk factor of CiLI in this paper. Emerging evidence has noted that both mitochondria content and function are higher in females, Silaidos et al. (2018) which can justify why male patients are more susceptible to developing CiLI.

4.3. Comorbidities

It has been demonstrated that patients with diabetes mellitus, hypertension, cardiovascular disease, or cancer are at a greater risk of developing CiLI (Shen et al., 2021). However, the underlying mechanisms are remained to be defined. Available studies have demonstrated that mitochondrial biogenesis is impaired in patients with diabetes mellitus in terms of redox homeostasis, fission/fusion, and respiratory chain activity (Rovira-Llopis et al., 2017). Also, it has been demonstrated that patients with essential hypertension and cardiovascular disorders have some extent of mitochondrial dysfunction (Ding et al., 2013; Yang et al., 2022). Therefore, patients' comorbidities, as risk factors of CiLI, are justifiable through mitochondrial dysfunction.

4.4. Parenteral nutrition

A large cohort study on hospitalized patients with COVID-19 indicated that patients receiving intravenous nutrition are at greater risk for developing CiLI (Zhang et al., 2021). However, the underlying mechanism was not outlined. In a rat model receiving parenteral nutrition —containing dextrose, amino acids, fat emulsion, minerals, and vitamins— the investigators found degrees of hepatic mitochondrial dysfunction (Katayama et al., 1990). In this study, the hepatocytes' mitochondria of rats receiving parenteral nutrition had a lower capacity for oxidative respiration and ATP production. The detrimental effects of parenteral nutrition on mitochondria activity may justify how it increases the risk of liver injury in patients with COVID-19.

4.5. Medications

Hepatotoxicity is an adverse effect of a subset of drugs that COVID patients receive during hospitalization. This issue complicates the clinical judgment on the reason for CiLI. This section outlines how the common medications administered for patients with COVID-19 can damage liver tissue and how mitochondria can be involved in this process.

4.5.1. Antivirals

In a retrospective study on 192 hospitalized COVID-19 patients, Zhan et al. found that the administration of ritonavir (a protease inhibitor) is a significant risk factor for CiLI (Zhan et al., 2021). It has been demonstrated that ritonavir can dysregulate the mitochondrial membrane potential, which results in hepatocytes apoptosis following the release of mitochondrial cytochrome *c* into the cytosol (Ganta and Chaubey, 2019). Studies on the clinical safety of other antiviral agents used in patients with COVID-19 have demonstrated their potential hepatotoxicity. For example, remdesivir (an RNA-dependent RNA polymerase inhibitor) can damage liver tissue, usually in the form of mild-to-moderate elevation in transaminases (Aleem et al., 2021). Besides viral RNA, remdesivir can also inhibit the human mitochondrial RNA polymerase. This interference leaves open the possibility of mitochondrial toxicity. An experimental study on marine renal and cardiac cells demonstrated that remdesivir disrupted the metabolism and proliferation of kidney cells and reduced the heartbeat and contractility. These adverse effects were due to interference with mitochondrial membrane potential and respiratory chain (Merches et al., 2022). However, in another study on hepatocytes, remdesivir's inhibitory effect on mitochondrial RNA polymerase was weak and did not translate to the defect in mitochondrial respiration (Bjork and Wallace, 2021). These findings demonstrated that different tissues have different sensitivity to the mitochondrial toxicities of remdesivir.

4.5.2. Antibiotics

In a large cohort study, Zhang et el. noted that antibiotic administration significantly increased the risk of liver damage in hospitalized patients with COVID-19 (Zhang et al., 2021). However, the study did not outline the name/group of antibiotics. For hospitalized patients with COVID-19, antibiotics are commonly applied for its complications, such as bacterial pneumonia. To this end, the common antibiotics are vancomycin, oxacillin, and amoxicillin/clavulanate (for methicillin-susceptible staphylococcus aureus [MSSA]), linezolid (for methicillin-resistant staphylococcus aureus [MRSA]), and colistin (for acinetobacter baumannii) (Posteraro et al., 2021). Among these, the hepatocytes' mitotoxicity of vancomycin (Wu and Zhou, 2022), amoxicillin/clavulanate (Oyebode et al., 2019), and linezolid (De Vriese et al., 2006) has been evidenced. Therefore, commonly used antibiotics during the COVID-19 course can lead to CiLI by dysregulating the mitochondrial function of hepatocytes.

5. How boosting mitochondria can protect liver from COVID-induced injury

In Zhang et al.'s cohort, three hepatoprotective agents (diammonium glycyrrhizinate, magnesium isoglycyrrhizinate, and polyene phosphatidylcholine) significantly reduced the risk of CiLI (Zhang et al., 2021). However, the underlying mechanisms were not noted. This section describes the effects of the aforementioned agents on mitochondria biogenesis and how this action can reduce the incidence/severity of CiLI.

Diammonium glycyrrhizinate (DaG) is a glycyrrhizic acid derived from the root of Radix Glycyrrhizae. It has been shown that DaG improves the cellular peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) content (Zhu et al., 2012), which in turn upregulates mitochondria biogenesis (Onishi et al., 2014). Magnesium isoglycyrrhizinate (MgIG) is a novel preparation of glycyrrhizic acid. MgIG can improve mitochondria biogenesis through upregulating 5′-adenosine monophosphate-activated protein kinase (AMPK) expression (Herzig and Shaw, 2018; Jiang et al., 2020). Polyene phosphatidylcholine, a phospholipid enriched in polyunsaturated fatty acids, has a similar mechanism of action to boost mitochondrial metabolism via AMPK upregulation (Herzig and Shaw, 2018; Lu et al., 2022). But how can mitochondrial activation reduce the risk of CiLI?

(1) As noted in Section 1, SARS-CoV-2 can modulate the hepatocytes' mitochondrial function to impede a proper innate immune response. Hence, patients with mitochondrial dysfunction are more susceptible to SARS-CoV-2 invasion due to an imperfect frontline immune reaction (Morio et al., 2021). Therefore, more potent mitochondria can reduce the severity of developing COVID-19, which further reduces the risk of CiLI. Another possible mechanism is by impeding/reducing the COVID-associated cytokine storm. (2) As noted in Section 3.2, cytokine storm can lead to mitochondrial dysfunction, which in turn aggravates the release of IFN-1 from pDCs (Rebbapragada et al., 2016). Therefore, boosting mitochondrial activity can break this vicious cycle and

alleviate/prevent the massive release of cytokines. (3) Another mechanism by which boosting mitochondrial metabolism can inhibit hepatocyte damage is by inhibiting COVID-induced ferroptosis. Functional mitochondria enhance the cellular glutathione level (Taghizadeh-Hesary et al., 2022), directly inhibiting cellular lipid peroxidation through glutathione-GPX4 pathway (Maiorino et al., 2018). (4) Section 3.1 denoted how COVID-induced mitochondrial-DAMPs release can increase SARS-CoV-2 entry into hepatocytes. Improving mitochondrial function can disrupt this vicious cycle by safely recycling the damaged mitochondria by mitophagy. Functional mitochondria can serve as a regulator of mitophagy given the following two assumptions: (a) hypoxia-inducible factor 1 (HIF-1) is one of the primary regulators of autophagy in cancer cells (Nazio et al., 2019), (b) HIF-1 requires mitochondrial support to function (Van Gisbergen et al., 2020). This approach has been applied in recent studies using hydroxytyrosol. Dong et al. examined hydroxytyrosol, derived from olive oil, in the setting of NASH. This study showed hydroxytyrosol can alleviate NASH by inducing mitophagy upon mitochondrial activation through the AMPK/PINK1 pathway (Dong et al., 2022).

Enhancing the mitochondria metabolism can impede/reduce the devastating effects of SARS-CoV-2 on hepatocytes' mitochondria, preventing/alleviating the CiLI. To this end, it is recommended to apply strategies to enhance mitochondria content and activity. The mitochondria quality can increase by two strategies; (1) improving the lifestyle by regular exercise (Memme et al., 2021), specific diets (low-specific dynamic action diet (Luoma et al., 2016), branched-chain amino acid-rich diet (D'Antona et al., 2010), and Mediterranean diet (Khalil et al., 2022); good sleep (Rodrigues et al., 2018), healthy weight (de Mello et al., 2018), alcohol abstinence (Abdallah and Singal, 2020), and smoking cessation (Malińska et al., 2019); and (2) mitochondria boosting agents (e.g., Coenzyme Q10, activators of adenosine AMPK, acetyl-L-Carnitine; mammalian target of rapamycin [mTOR], PGC-1α, etc.) (Chamoto et al., 2017; Pizzorno, 2014), as denoted in the previous paragraph. In addition, recently, liver-targeted nanomedicines have been applied to improve the mitochondrial function of hepatocytes (Wu et al., 2019). Exercise is an established non-pharmacological method to maintain mitochondrial integrity. It has been demonstrated that exercise can improve mitochondrial quality control, which further improves the quality of mitochondrial biogenesis, trafficking, and repair (Sorriento et al., 2021). In addition, the human gut microbiota is another modulator of mitochondrial fitness. It has been demonstrated that microbiota-derived metabolites are necessary for the proper action of mitochondrial metabolisms, including glycolysis, tricarboxylic acid (TCA) cycle, oxidative phosphorylation, as well as amino acid and fatty acid metabolism. In addition, gut microbiota-derived short-chain fatty acids can enhance mitochondrial function by activating the AMPK pathway (Imdad et al., 2022). The mitochondrial boosting strategies are diverse. Detailed information is presented in the following sources (Pizzorno, 2014; Burtscher et al., 2022).

6. Conclusions

This review noted how mitochondrial dysfunction leads to deranged liver function in the context of COVID-19. This hypothesis is originated from the crucial role of mitochondria in the metabolism of hepatocytes and further justified by the histopathologic and transcriptomic appearances of CiLI. Recent evidence demonstrated that SARS-CoV-2 enters its genome into the hepatocytes' mitochondria, leading to mitochondrial malfunction. In other words, SARS-CoV-2 exploits host cells' mitochondria for its replication. This article indicated how the interaction between SARS-CoV-2 and mitochondria can justify the risk factors of CiLI. It also illustrated how SARS-CoV-2 can directly damage the hepatocytes' mitochondria and how mitochondrial dysfunction can aggravate the COVID-associated cytokine storm. Preventing the devastating impacts of SARS-CoV-2 on hepatocytes' mitochondria is a potential area of research to prevent and treat liver damage in the context of COVID-19. Detailed and comprehensive studies are required to clarify the interaction between SARS-CoV-2 and hepatocytes' mitochondria.

Authors' contributions

F.T-H and H.A. designed the research; F.T-H acquired data. F.T.H. performed the research; F.T.H. wrote the paper; H.A. provided funding; supervised the research. All authors gave final approval of the version to be submitted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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