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Roles of mitochondrial DNA in dynamics of the immune response to COVID-19

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ABSTRACT

Mitochondria dynamics have a pivotal role in many aspects of immune function. Viral infections affect mitochondrial dynamics and trigger the release of mitochondrial DNA (mtDNA) in host cells. Released mtDNA guides the immune response towards an inflammatory response against pathogens. In addition, circulating cell-free mtDNA (ccf-mtDNA) is considered an invaluable indicator for the prognosis and severity of infectious diseases. This study provides an overview of the role of mtDNA in the dynamics of the immune response to COVID-19. We focused on the possible roles of mtDNA in inducing the signaling pathways, and the inflammasome activation and regulation in SARS-CoV-2. Targeting mtDNA-related pathways can provide critical insights into therapeutic strategies for COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) as the result of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a catastrophic effect on the worldwide in the 21st century. The heterogeneous clinical spectrum, ranging from asymptomatic and mild upper respiratory tract illness to severe interstitial pneumonia with respiratory failure and even death, has introduced major challenges to the management of the COVID-19 pandemic (Wang et al. 2020). On the other hand, the differential immune response can contribute to the inter-individual variations in the clinical manifestations of infectious diseases (Verhein et al. 2018).

Cell death ensures the survival of multicellular organisms against viral infections. Apoptosis and programmed necrosis limit pathogen replication in infected cells, while the release of damage-associated molecular patterns (DAMPs) promoting the inflammatory and innate responses in the host. DAMPs serve as endogenous ligands for interactions with Toll-like receptors (TLRs). TLRs play potent roles in inducing innate responses by promoting the expression of inflammatory cytokines (Upton and Chan 2014). Strong evidence suggests that mitochondria facilitate effector responses of the immune system. Mitochondrial DAMPs (mtDAMPs) are the potent immunological activators

Abbreviations: mtDNA, mitochondrial DNA; ccf-mtDNA, circulating cell-free mitochondrial DNA; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory coronavirus 2; DAMP, damage-associated molecular pattern; TLR, Toll-like receptor; Mt-DAMP, mitochondrial- damage-associated molecular pattern; ICU, intensive care unit; MAVS, mitochondrial antiviral signaling; HIV, human immunodeficiency virus; HPV, human papillomavirus; ISG, interferon stimulatory gene; ROS, reactive oxidative stress; ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane serine protease 2; PRR, pathogen-recognition receptors; MyD88, myeloid differentiation factor 88; cGAS, Cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) (cGAMP) synthase; STING, stimulator of interferon genes; ER, endoplasmic reticulum; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; ORF, open reading frame; NBD, nucleotide binding domain; LRR, leucine rich repeat; NLR, nucleotide binding domain and leucine rich repeat; mtROS, mitochondrial reactive oxygen species; lncRNA, long non-coding RNA; AIM2, Absent in melanoma 2; GSDMD, gasdermin D; MSC, Mesenchymal stem cell.

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and released mtDAMPs such as N-formyl peptides, cytochrome *c*, cardiolipin, and mitochondrial DNA (mtDNA) from the damaged or dying cells into the cytoplasm or circulation can influence immunity (Piantadosi 2020). Biological behaviors, such as cell necrosis and apoptosis can damage integrity of the cell membrane. Fragments of the mtDNA are subsequently released into the extracellular environment, such as blood or urine, and also stimulate systemic inflammation (De Gaetano et al. 2021). Several studies highlight the pivotal role of the mtDNA in inflammatory cell activation during viral infections (Kausar et al. 2020; Lai et al. 2018; West et al. 2011).

Increasing evidence supports the significant association between the level of ccf-mtDNA in plasma and mortality rate in critically ill patients (Harrington et al. 2019). Recent evidence suggests that mitochondrial dysfunction have an essential role in COVID-19 pathogenesis. The recent finding showed that high levels of ccf-mtDNA at the time of hospitalization elevated the probabilities of intensive care unit (ICU) admission and heightened the risk of death (Ayala et al. 2020; Saleh et al. 2020; Scozzi et al. 2021; Valdés-Aguayo et al. 2021). In the present review, we have attempted to highlight the possible roles of mtDNA as a mtDAMP in regulating the immune response and inflammatory reactions against COVID-19 infection. We have discussed the potential role of mtDNA in the induction of its related signaling pathways in cells infected with SARS-CoV-2. Moreover, we have pointed the possible role of mtDNA in inducing the biological processes and molecular mechanisms of inflammation in COVID-19.

2. Mitochondria trigger innate immunity during viral infections

Mitochondria are functionally versatile organelles and impacts cellular homeostasis, metabolism, and innate immune signaling. They play central role in the host defense against many diseases and are central participants in the induction of cell death, as well as in immune signaling pathways. Viral infections target mitochondrial function directly by viral proteins or physiological and biochemical alteration during the infections. Therefore, mitochondrial dynamics can be the major determinant of the outcome of viral infections (McWhirter and Maniatis 2005).

Activation of the immune responses through mitochondrial antiviral signaling (MAVS) serves as the crucial cellular antiviral signaling pathway that induces the host's innate immunity against viral infection (Belgnaoui et al. 2011; Seth et al. 2005). Innate immune responses are triggered by mtDAMPs which are released from damaged or dying cells into the circulation of the host (Elesela and Lukacs 2021; Khan et al. 2015; West et al. 2011). Several potent immunological activators can induce the secretion of various proinflammatory cytokines causing cytokine storm (Hauser and Otterbein 2018; Itagaki et al. 2021) and increased plasma levels of extracellular mtDNA during various viral infection, such as HIV and HPV (Cossarizza et al. 2011; Feng et al. 2016).

The release of mtDNA into the cytoplasm and out into the extracellular milieu induces different pattern recognition receptors and innate immune responses (Riley and Tait 2020). These processes elicit the transcription of numerous interferon stimulatory genes (ISGs) that have potential and robust antiviral properties (Riley and Tait 2020). Some viruses can down-regulate interferon proinflammatory response by inducing mitochondrial fusion (Khan et al. 2015). Also, the inhibition of apoptosis as the result of imbalanced mitochondrial fission and fusion can ensure the survival of viral particles for longer (Ren et al. 2020). However, the maintenance of mitochondrial integrity is essential for adequate innate immune system responses and effective suppress of the cytokine storm in viral infections (Koshiba et al. 2011).

3. Mitochondrial perspective of COVID-19

Clinical, immunological, and pathologic features of COVID-19 highlight the crucial role of the inflammatory state termed as the "cytokine storm" in the severity, and mortality rate of COVID-19 (Yuki et al. 2020). This inflammatory state is associated with diverse deleterious pathophysiological events such as reactive oxygen species (ROS) production, and dysregulation of iron homeostasis in COVID-19 patients. Mitochondrial dysfunction affects iron homeostasis and oxidative stress in viral infections (Drakesmith and Prentice 2008; Saleh et al. 2020; Silwal et al. 2020).

Mitochondrial dysfunction is strongly associated with aging. The speed and strength of immune response weaken due to the loss of certain immune tissues, as well as poorer energy metabolism at the cellular level (Wang and McLean 2022). Increased age correlates with the accumulation of mtDNA mutations which associate with the decline in mitochondrial levels and function (Chinnery et al. 2002). Given the evidence for mitochondrial involvement in aging and age-related diseases, mtDAMPs can be released from the mitochondrion and trigger immune and inflammatory responses in the elderly (Salminen et al. 2012). Also, mtDAMPs induce the inflammasome-associated caspases and mediate the maturation and release of the proinflammatory cytokines in advanced age (Furman et al. 2017). Steadily increase of circulating mtDNA in the cytoplasm of elderly people suggests a causal role of extracellular mtDNA in age-related immune activation (Pinti et al. 2014). Based on our current knowledge, various age-related comorbidities such as diabetes, obesity, hypertension, dementia, coronary heart disease, chronic obstructive pulmonary disease, metabolic syndrome, and neurological diseases can play pivotal roles in COVID-19 severity and mortality amongst the elderly patients (Yang et al. 2020; Zhang et al. 2020a). The considerable role of mtDNA in inducing innate immunity and inflammatory responses can be the basic mechanism that contributes to the severity and lethality of COVID-19 in older patients (Ayala et al. 2020; Ganji and Reddy 2021).

The genome organization of SARS-CoV-2 is similar to other coronaviruses, which include a positive single-stranded RNA β-coronavirus. So, based on available data for the SARS-CoV-1, it seems that SARS-CoV-2 may hijack the mitochondria-targeted pathways to viral advantages such as survival, virulence and propagation (Saleh et al. 2020). Recent gene expression profiling of SARS-CoV-2 infection indicated that the imbalance in mitochondrial dynamics may stimulate viral replication by manipulating the immune responses and metabolism (Singh et al. 2020). The interaction between a number of SARS-CoV-2 and mitochondrial proteins promotes virus replication in cells. SARS-CoV-2 could also promote viral replication and immune evasion by inhibition of mitochondrial antiviral signaling protein (MAVS) (Gordon et al. 2020).

SARS-CoV-2 cell entry depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) for entry. It enters the cells by binding to ACE2 in a cholesterol-rich microdomain as the receptor (Hoffmann et al. 2020). Substantial genetic variation in the ACE2 gene is reported among world populations (Srivastava et al. 2020). Interestingly, ACE2 variation can also affect mitochondrial function (Shi et al. 2018). Thus, the mitochondrial function can be under the control of the variant and expression levels of the ACE2 gene (Singh et al. 2020). Understanding the relevance of mitochondrial dysfunction may shed light and elucidate the pathogenesis mechanisms and inter-individual variations in clinical manifestations of COVID-19. Also, the versatile nature of mitochondria can provide invaluable insights into the sophisticated mechanisms of immunomodulation, diagnostic and therapeutic targets to combat SARS-CoV-2 infection.

4. MtDNA-related signaling pathways in COVID-19

Recognition and elimination of an invading pathogen are directly dependent on balanced immune regulation. MtDNA is one of the intrinsic sources of self-nucleic acid with immunostimulatory capacity. Loss of mitochondrial integrity can allow the release of mitochondrial nucleic acid into the cytosol. Subsequently, the interaction of mtDNA with cytosolic receptors induces specific immune responses (Schafer

et al. 2016). MAVSs mediate the induction and regulation of interferon responses to viral infections (Ablasser and Hur 2020; Vazquez and Horner 2015). The following sections summarize the possible role of mtDNA in the dynamics of the immune signaling pathways in COVID-19.

4.1. MtDNA -associated TLRs signaling pathways in COVID-19

Members of the TLRs family belong to a class of pathogen-recognition receptors (PRR) that detect conserved viral nucleic acid that leads to innate immune activation and orchestration of the adaptive immune response (Carty and Bowie 2010).

The detail of molecular mechanisms of COVID-19 pathogenesis is still elusive. Therefore, our understanding of molecular signaling pathways of COVID-19 arises from the available data about SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Previous studies highlight the important role of type I interferon in the systemic inflammatory response during infection with SARS-CoV and MERS-CoV (Angelopoulou et al. 2020; Moreno-Eutimio et al. 2020).

Five mammalian Toll-like receptors (TLRs), including TLR3, TLR7, TLR8, TLR9, and TLR 13 can be activated by nucleic acid ligand. TLR9 was first identified as a DNA sensing receptor in immune cells. Specific affinity of TLR9 for unmethylated cytosine and guanine (CpG) nucleotides and the bacterial ancestry of mitochondria explain the mtDNA binding to TLR9. TLR9 activates the innate immune system by binding to mtDNA on immune cells. Therefore, in viral infections, when mtDNA is released into the circulation during mitochondria-induced cell death, it can elicit the immune response by binding to TLR9 (Barton et al. 2006; Zhang et al. 2010). The high number of unmethylated CpG motifs in genetic material of SARS-CoV-2 leads to TLR9 activation in many cells types during COVID-19 (Digard et al. 2020). In addition, activation of TLR9 can trigger hyper inflammation and thrombotic complications caused by SARS-CoV-2 infection (Bezemer and Garssen 2021). TLR9 triggers an inflammatory downstream response, myeloid differentiation factor 88 (MyD88) (Cuevas et al. 2021). Recent findings demonstrated that an elevated level of ccf-mtDNA in endothelial cells promotes activation of TLR9 inflammatory responses, via NF-kB signaling and IL-6 production in SARS-CoV-2 infection (Costa et al. 2021); Fig. 1 illustrates this pathway. Investigation of inherent differences in the immune system of black Americans detected significant elevation of TRL9 expression in SARS-CoV-2 infection. Interestingly, this finding may also explain the susceptibility to develop a rapid and more aggressive cytokine storm in different ethnicities (Tal et al. 2020).

4.2. MtDNA -associated cGAS-STING signaling pathway in COVID-19

Cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) (cGAMP) synthase (cGAS) is a cytosolic DNA sensor, which produces the second messenger cGAMP. This signaling pathway induces type I interferons and other immune mediators through activation of stimulator of interferon genes (STING) by cGAMP (Zhang et al. 2020c). STING is predominantly an endoplasmic reticulum (ER) - mitochondria associated membranes protein that can orchestrate diverse immune responses, including proinflammatory cytokine responses, interferon responses, apoptosis and autophagy (Smith 2021).

The cGAS-cGAMP-STING pathway is a major pathway for detecting pathogen-derived DNA in vertebrates. However, the role of the cGAS pathway is not limited to antimicrobial defense. cGAS can be activated by self-DNA, including genomic and mitochondrial DNA (Zierhut and Funabiki 2020). cGAS is a universal DNA sensor and cannot discriminate self from non-self DNA. Pathological stimulation induces mtDNA release into the cytosol, which is recognized by the DNA sensor cGAS, and activates the cGAS-cGAMP-STING pathway (Ablasser and Chen 2019; Li and Chen 2018). A Recent analysis of the level of ccf-mtDNA and degree of STING activation during sepsis-induced acute lung injury indicated that STING activation plays a pivotal role in mtDNA-mediated lung injury by inducing an inflammatory storm and disturbing autophagy. These findings highlighted unique features of ccf-mtDNA that are recognized by the STING pathway of macrophages in sepsis-related acute lung injury. These findings elucidate the role of cGAS-STING-mediated mtDNA pathway in self-injurious and anti-regenerative responses of the endothelium during murine acute lung injury (Huang et al. 2020; Liu et al. 2021). Moreover, self-DNA leaked from mitochondria can serve as a cGAS ligand to activate this pathway in lung diseases such as cystic fibrosis, chronic obstructive pulmonary disease,

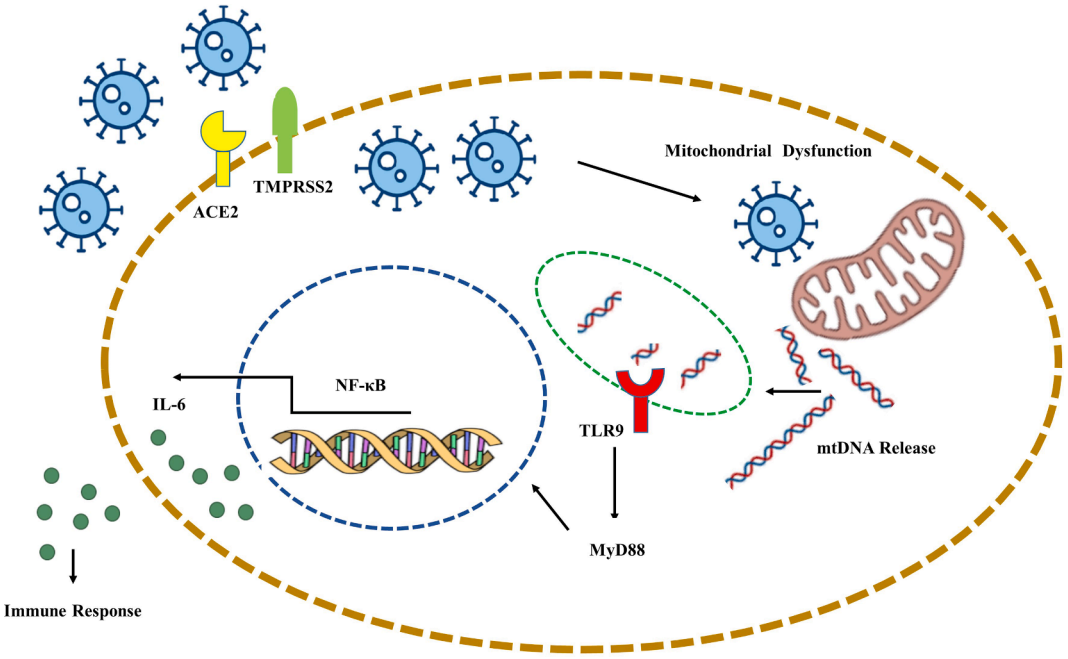

Fig. 1. Schematic signaling pathway for the role of mtDNA in the activation of TLR9 in COVID-19. ACE2 and TMPRSS2 are critical players for SARS-CoV-2 cell entry. SARS-CoV-2 induces the release of mtDNA as the result of mitochondrial dysfunction. The transportation of mtDNA fragments to endosomes exposes them to TLR9. TLR9-MyD88-dependent activation of the NF-κB pathway induces the immune response by production of IL-6.

idiopathic pulmonary fibrosis, and asthma (Ma et al. 2020).

SARS-CoV-2 ORF9b protein interacts with multiple components of the several signaling pathways such as STING, and negatively regulates antiviral immunity and thus facilitates viral replication (Han et al. 2021). SARS-CoV-2 could induce the formation of multinucleate syncytia by cell–cell fusion during infection. These micronuclei could provide an efficient way for the SARS-CoV-2 RNA virus to activate IFN response via the cGAS-STING signaling pathway (Ren et al. 2021). Analysis indicated that regulating the upstream of the cytokines production such as the cGAS-cGAMP-STING pathway could consider as a potential therapeutic target preventing cytokine storm in COVID-19 (Deng et al. 2020). There is evidence to suggest that most caspase family members can regulate the cGAS–STING signaling pathway negatively. Considering the interactions between the cGAS–STING signaling and COVID-19, it seems that the inhibition of caspase-mediated cleavage of cGAS–STING could be beneficial for reducing tissue damage in responses to SARS-CoV-2 infection (Xiong et al. 2021).

5. MtDNA and inflammasome activation and regulation in COVID-19

Inflammasomes are the multiprotein oligomers that act as the innate immune system receptors when encountered with pathogens and some host proteins. Both exogenous and endogenous ligands can activate inflammasome and inflammatory cascade (Zheng et al. 2020). The inflammasomes regulate the activation of the Caspase-1, which induces the cell death process known as pyroptosis, and secretion of interleukins (de Zoete et al. 2014; Guo et al. 2015). There is a two-way relationship between inflammation and mitochondrial dysfunction. Activation of the inflammasome activates inflammatory mediators that inhibit the production of ATP in the mitochondria, which in itself accelerates the production of ROS in the mitochondria and is the cause of further changes in mitochondrial metabolism (Kowaltowski et al. 2009). Mitochondrial dysfunction leads to production of more ROS, subsequent mtDNA damage, mtDNA release, and inflammasome activation (Naik and Dixit 2011). SARS-CoV-2 infection can engage inflammasome and trigger pyroptosis in human monocytes (de Rivero Vaccari et al. 2020; Ferreira et al. 2021). Recent findings highlighted the effect of COVID-19 on mtDNA and inflammasome activation is the localization of viral RNA in the host mitochondria and use of host mitochondria to propagate the virus, which affects severity of infection (Burtscher et al. 2020). The insertion of viral RNA into the mitochondrial genome can directly enhance the mitochondrial function in favor of the proliferation of COVID-19 by altering open reading frames (ORFs) such as ORF-9b. The growth of the virus, as previously mentioned, can release mtDNA and lead to activation of the inflammasome and inflammatory cascade (Singh et al. 2020). Here, we reviewed the role of double-strand DNA-sensing inflammasomes in COVID-19.

5.1. MtDNA and NLRP3 inflammasome in COVID-19

The NLR (nucleotide-binding domain leucine-rich repeat containing) proteins are a family of innate immune receptors that contribute to the regulation and induction of antimicrobial immune responses (Ye and Ting 2008). The genomic mining of evolutionary conserved regions with structural similarity and functional overlaps has led to the discovery of a large gene family encoding proteins with a characteristic arrangement of NLR. There is several number of NLR proteins in mammalian cells (Elinav et al. 2011; Ting et al. 2008).

The NLRP3 is the key member of NLR proteins which actives in response to diverse stimuli. Both mtDNA and mitochondrial ROS (mtROS) directly induce the activation of NLRP3 inflammasome (Ye and Ting 2008). Mitochondrial dysfunction and programmed cell death lead to release of mtDNA into the cytosol. Ccf-mtDNA promotes activation of the NLRP3 inflammasome and triggered macrophages for orchestration of immune response (Shimada et al. 2012; Zhong et al. 2018). Genetic and pharmacological evidence elucidate the critical role of the NLRP3 inflammasome in the progression of several pulmonary diseases and viral and bacterial infections of the respiratory tract (De Nardo et al. 2014; Grailer et al. 2014). Activation of NLRP3 inflammasome by ccf-mtDNA can induce pulmonary inflammation and injury through TLR9, p38 MAPK and NF-κB pathways in macrophages (Wu et al. 2019).

Heterogeneous and inter-individual variations in clinical manifestations of COVID-19 patients could be attributed to deleterious effects of inflammasome activation, which is related to the fitness of the immune system of the (Fulop et al. 2017). Recent evidence suggested that SARS-CoV-2 might directly activate NLRP3 inflammasome and subsequent upregulation of downstream Caspase-1, and inflammatory cytokines in COVID-19 patients (Amin et al. 2021; Pan et al. 2021; van den Berg and Te Velde 2020). Fig. 2 illustrates the role of mtDNA in the activation of NLRP3 inflammasome in SARS-CoV-2 infection. Investigation of the effect of SARS-CoV-2 nucleocapsid protein (N) indicated that N protein could directly interact with NLRP3 and promote the assembly and activation of NLRP3 inflammasome in cultured cells and mouse models. As a result, large amounts of cytokines are released, which play a critical role in initiating “cytokine storm” in COVID-19. These findings suggest that SARS-CoV-2 N protein may cause lung injury by inducing the production of proinflammatory factors such as IL-1β and IL-6. Therefore, this kind of inflammasome appears to be a potential therapeutic target for COVID-19 (Pan et al. 2021). Overactivation of NLRP3 inflammasome in patients with uncontrolled diabetes could be one of the major contributing factors for COVID-19 severity (Lambadiari et al. 2020). Delay of INF-γ response and lower CD4 + and CD8 + cell numbers as the result of NLRP3 inflammasome overactivity may make diabetic patients vulnerable to adverse clinical outcomes in COVID-19 infection (Lambadiari et al. 2020). The crucial role of NLRP3 in the pathogenesis of SARS-CoV-2 highlights the therapeutic importance of the NLRP3 inflammasome in COVID-19. Therefore, it seems that pharmacological inhibitors and long non-coding RNAs (lncRNAs) might help reduce the clinical manifestations of SARS-CoV-2 (Freeman and Swartz 2020; Paniri and Akhavan-Niaki 2020; Shah 2020).

5.2. MtDNA and AIM2 inflammasome in COVID-19

Absent in melanoma 2 (AIM2) cytosolic innate immune sensors detect the presence of double-strand DNA, and lead to the assembly of the inflammasome. AIM2 inflammasome promotes the secretion of the cytokines IL-1β and IL-18 and also initiates pyroptosis.. AIM2 inflammasome plays a critical role as a guardian of cellular integrity in inflammatory and infectious diseases (Sharma et al. 2019).

Recent findings unraveled that ccf-mtDNA induces AIM2 inflammasome-dependent caspase-1 activation and IL-1β and IL-18 secretion in various human diseases such as type 2 diabetes, and nonalcoholic fatty liver disease (Bae et al. 2019; Cataño Cañizalez et al. 2018; Xu et al. 2021). Based on our current knowledge, influenza virus-induced oxidized mtDNA can stimulate AIM2-dependent IL-1β secretion in macrophages; in addition, AIM2 inflammasome plays a critical role in virus-induced lung injury and mortality (Moriyama et al. 2020; Zhang et al. 2017). Recent evidence showed that monocytes in the blood of patients with SARS-CoV-2 infection activate AIM2 inflammasome following the caspase-1, gasdermin D (GSDMD) cleavage and trigger immune response (Junqueira et al. 2021). Taken together, the findings of the current studies indicated that mtDNA could play a major role in the activation of AIM2 inflammasome and following inflammatory response and cytokine storm during severe COVID-19.

6. Mitochondria, as an Emerging therapeutic target in COVID-19

There are many avenues involving mitochondria and their roles in the pathogenesis of SARS-CoV-2. Emerging evidence suggests that COVID-19 highjacks mitochondria of immune cells. Mitochondria centralize several critical innate immune responses through the

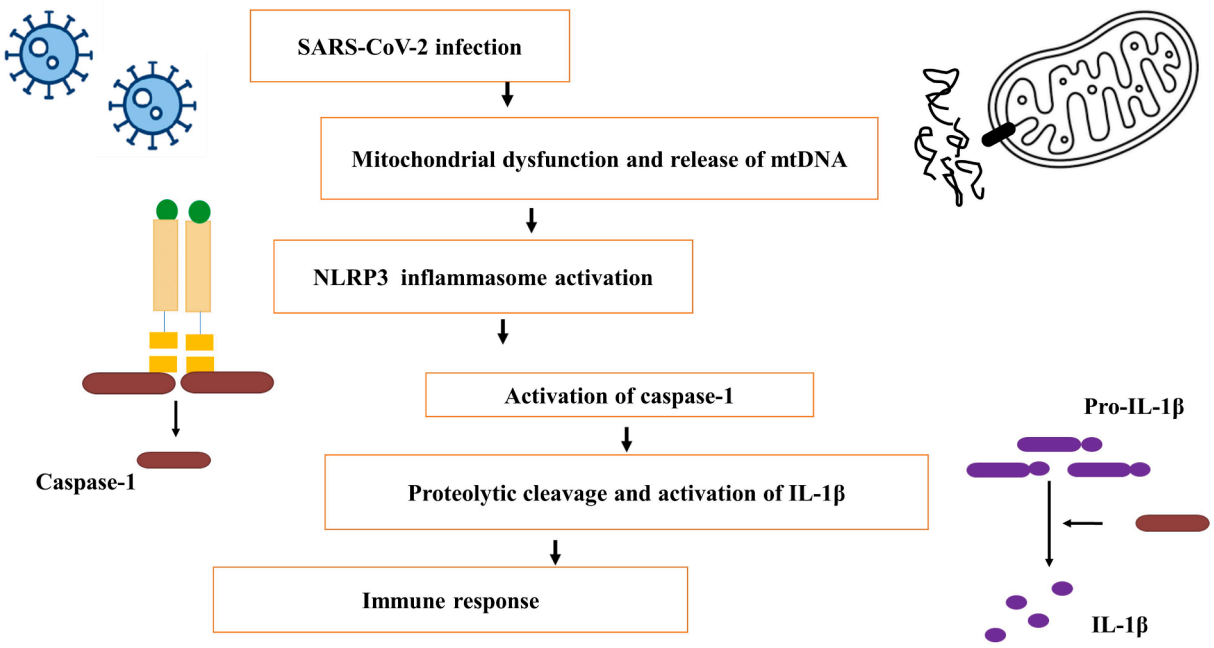

Fig. 2. Schematic illustrations of the role of mtDNA in the activation of NLRP3 inflammasome in COVID-19. Activation of NLRP3 inflammasome can be a result of mtDNA release in SARS-CoV-2 infection. Subsequent regulations activate Caspase-1, which is involved in the processing of pro-IL-1β to active secreted IL-1β. IL-1β play a pivotal role in the orchestration of innate and adaptive immune responses.

activation of MAVSs and inflammasome-mediated pathway in viral infections (McWhirter and Maniatis 2005). Therefore, the role of mitochondria should not be ignored in developing new therapeutic approaches for COVID-19.

Melatonin is a mitochondrial targeting antioxidant that seems to play a key role in suppressing COVID-19 infection by suppressing the cell apoptosis and blocking the inflammasomes activation (Zhang et al. 2020b). The crucial role of mitochondria in inducing immune responses by activation of MAVSs and inflammasome formation indicated that increased expression of MAVS proteins could provide promising insights into the treatment of COVID-19 (Babajani et al. 2021). Recent findings demonstrated that the *in vivo* transferring of healthy mitochondria to the damaged cells by manipulated mesenchymal stem cells (MSCs) that express SARS-CoV-2 viral spike protein and have overexpressed MAVS protein can boost innate immune responses in a targeted manner (Babajani et al. 2021). Also, considering the bacterial origin of mitochondria, the application of uncovered mitochondrial DNA can regulate inflammation, repair the damaged tissue, and control the pathogenesis of COVID-19 (Saleh et al. 2020). Therefore, designing the appropriate carriers raises the chance of targeted therapy of susceptible subjects and improves the outcome. Finally, the crosstalk between mitochondria and COVID-19 describes the most promising therapeutic strategies for treatment of COVID-19.

7. Conclusion

Mitochondria participate in a broad range of immune pathways and inflammasome activation during the antiviral immune response. mtDAMPs released in viral infections, such as mtDNA, can elicit immune response. Moreover, elevated levels of ccf-mtDNA have been reported as early indicator of the prognosis and severity in viral infections and COVID-19. We discussed the latest findings concerning the central role of mtDNA-related signaling pathways in COVID-19. Based on our current knowledge, mtDNA is recognized by TLR9 and cGAS-STING, which serve as fundamental mtDNA-related signaling pathways in the induction of immune response and aggressive cytokine storm during SARS-CoV-2 infection. Activation of NLRP3 and AIM2 inflammasomes stimulate the production of the proinflammatory cytokines and orchestrate the innate and adaptive immune responses. However, further studies are needed to delineate the detail of the molecular mechanism towards therapeutic approaches for COVID-19.

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CRediT authorship contribution statement

Ata Mahmoodpoor: Project administration, Conceptualization, Funding acquisition. **Sarvin Sanaie:** Project administration, Conceptualization, Funding acquisition, Writing – review & editing. **Zoherh Ostadi:** Writing – review & editing. **Maqsoud Eskandari:** Writing – review & editing. **Nazila Behrouzi:** Writing – review & editing. **Roqayyeh Asghari:** Writing – review & editing. **Ahmad Zahirnia:** Investigation, Validation. **Nasim Sohrabifar:** Conceptualization, Investigation, Validation, Writing – original draft. **Somayeh Kazeminasab:** Conceptualization, Investigation, Validation, Writing – original draft.

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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