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Cellular and molecular insights into microbiota-mitochondria interplay, therapeutic biomarkers and interventional approaches in COVID-19: A review

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Abstract: The persistent global pandemic, COVID-19, stems from the pathogenic influence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), yielding an unprecedented worldwide crisis. With reference to a WHO report, the count of COVID-19 cases had exceeded 754 million by February 03, 2023. Intriguingly, emerging research has spotlighted the intricate interplay of gut microbiota and mitochondrial entities, acting as potent immunomodulatory factors at the cellular and molecular levels. This interconnection operates through a series of dynamic mechanisms. SARS-CoV-2 infection perturbs the delicate equilibrium of gut microbiota, leading to dysbiosis —a signature biomarker. This imbalance is intrinsically linked to exacerbated COVID-19 progression. Mechanistically, this microbial dysbiosis triggers aberrant immune responses, marked by cytokine storms, while also inducing mitochondrial dysfunction. Mitochondrial activities crucial to energy production and immunoregulation are compromised. This dual perturbation of microbiota and mitochondria contributes to disease severity. This review provides a comprehensive overview of these interconnected mechanisms, illuminating how microbiota-mitochondria interplay serves as both a diagnostic biomarker and a promising therapeutic target in the realm of COVID-19.

Introduction

SARS-CoV-2 (formerly known as 2019-nCoV) virus is the cause of the highly contagious COVID-19 respiratory disease. In late 2019, the virus was first reported in China and rapidly spread worldwide through close human interactions to become a pandemic (Hu *et al.*, 2021). The worldwide economy, societies, and people are all highly affected by COVID-19. Over 220 million people were infected in the COVID-19 pandemic, and over 4.5 million have died since September 2021 (Mehta *et al.*, 2021). The pandemic has also disrupted healthcare systems, caused widespread economic hardship, and led to social and political unrest in some areas. Gastrointestinal symptoms such as diarrhea, nausea, and vomiting are observed in many COVID-19 patients (Mehta *et al.*, 2021). The human intestinal microbiota contains over 1500 microbial species that are distributed in hundreds of phyla (Mazzarelli *et al.*, 2022). The microbiota is composed of trillions of microbes, including not only bacteria but also fungi, archaea, viruses, or protozoans. It is an extremely diverse ecosystem inhabited by a variety of microbes that colonize specific locations (De and Dutta, 2022). The gut microbiota (GM) has a lot of important functions in humans, which include the development of the innate and adaptive immune system, maintenance of immunological tolerance, protection against bacterial infections by colonizing mucosal surfaces, the creation of various antibacterial agents, and sustaining healthy and normal gut physiology (Belkaid and Hand, 2014). Further, the microbiota plays a crucial role in digestion and metabolism, while controlling epithelial cell differentiation and proliferation, altering insulin resistance as well as increasing secretion, thus affecting brain-body communication and hence the psychological and neurological functions of the host (Nagata *et al.*, 2023). The GM dysregulation affects the health of the host in many ways, such as the gut-brain axis, and the absorption of energy, short-chain fatty acids (SCFAs), choline, bile acids, to name a few. Nevertheless, there is still a long way to go before we fully understand the

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mechanisms associated with GM in terms of diseases in humans (Gomaa, 2020; Chen *et al*., 2021).

The mitochondrion is a double-membrane organelle that performs a variety of functions, including steroid hormone and heme production, calcium and iron buffering, reactive oxygen species (ROS) signaling, and energy supply, and is involved in cell death and survival signaling (Srinivasan *et al*., 2021). The mitochondria, cellular metabolic generators, are crucial in regulating how cells proliferate, die, and maintain their redox state (Handy and Loscalzo, 2012). Cardiolipin and mitochondrial DNA (mtDNA) entry into the matrix of the cell and out of the cell could function as damage-associated molecular patterns (DAMPs), which might elicit an innate inflammatory response (Grazioli and Pugin, 2018).

In mammalian cells, the mitochondrion is a substantial generator of ROS. Therefore, the cytokine storm observed in COVID-19 includes the mitochondrion (Alfarouk *et al*., 2021). Many research investigations have demonstrated how impaired mitochondria affect the immunological outcome. For instance, according to a recent study, it was reported that during COVID-19, the pro-inflammatory mediators interleukin (IL)-6 and IL-12 and several chemokines such as chemokine (C-X-C motif) ligand (CXCL)-20, chemokine (C-C motif) ligand (CCL)3, CCL8, and CCL4 were produced at elevated levels in human alveolar epithelial cells due to dysfunctional mitochondria (Wang *et al*., 2019; Burtscher *et al*., 2020; Chen *et al*., 2020). All these cytokines were found to promote hyperinflammation. The production of tumor necrosis factor (TNF-α) and IL-1β results from the enormous rise in ROS that also causes such hyper-inflammation (Costela-Ruiz *et al*., 2020) The human microbiota is primarily located in the respiratory and gastrointestinal tracts (GIT), which is also a prime site to get SARS-CoV-2 infection given the high expression of angiotensin-converting enzyme 2 (ACE-2) and type 2 transmembrane protease serine (TMPRSS2), which mediate the viral entry into a host (Ni *et al*., 2020; Wiersinga *et al*., 2020). There is growing evidence that the hyper-inflammatory condition, i.e., a "cytokine storm," which causes significant systemic disturbances, is responsible for the accelerated progression of COVID-19 disease (Norsa *et al*., 2020; Chaves Andrade *et al*., 2020).

Microbiota: A Key Player in the Mitigation of COVID-19

The term "Gut microbiome" is a group of more than 1014 types of microbes found in the GIT, including bacteria, fungi, viruses, and eukaryotes (Zhang *et al*., 2022). Commensal microbiota modulates the innate immune response and helps prevent respiratory infections by providing an anti-viral response before viral infection; this phenomenon is known as "colonization resistance" (Wang *et al*., 2022). Gut microbiota performs various functions, one of which is to increase the resistance to infections by influencing type-1 interferon receptors located in respiratory epithelial cells, which respond promptly to viral infection via INF-α and INF-Secretin. Further, in CD4+, CD8+, and T-lymphocytes, (Jandhyala, 2015), the gut microbiota increases the expression of pro-IL-1β, pro-IL-18, and NLRP3 and suppresses that of IFN-YRI and MHC-1 molecules (de Oliveira *et al*., 2021). The health and nutrition of the gut flora are also essential (Valdes *et al*., 2018). They can metabolize indigestible substances like dietary fiber and endogenous intestinal mucus, which results in the formation of short-chain fatty acids (SCFA) such as metabolites like butyrate, acetate, and propionate and gas (Liu *et al*., 2022a). These metabolites maintain the integrity of the intestinal epithelial barrier (Chen *et al*., 2021).

Interestingly, a study conducted in the Chinese province of Guangdong revealed that COVID-19 suppresses the diversity of this commensal microbiota. To put it another way, opportunistic microorganisms proliferate at a predominant level while in contrast, the abundance of beneficial microbiota decreases (González *et al*., 2021; Wang *et al*., 2022). By downregulation of the immunomodulatory activity of the commensal microbiota, which favors dissemination and severity, these opportunistic microbiotas promote hyperinflammation via cytokine storm, often called systemic inflammatory response syndrome (SIRS) or inflammatory factor storm. This leads to microbiota dysbiosis, increased inflammation and GIT symptoms (Chen *et al*., 2021).

SARS-CoV-2 enters the epidermal cell by binding to ACE-2 and TMPRSS-2 surface receptors present in an epidermal cell, where the virus has undergone self-replication (Yeoh *et al*., 2021) This lead to the production and release of a large amount of viral proteins or formation of oligomers (processes for replication to utilize small building blocks to generate protein oligomers that assemble in multiple ways, thereby diversifying protein function and regulation) from infected epithelial cells. The innate cells (macrophages and dendritic cells) bind to pathogen associate molecular patterns (PAMP) via pattern-recognition receptors (PRR), which can be found associated with subcellular compartments, such as the cellular and endosomal membranes, the cytosol. Further, RIG-1 like receptor (RLR), Toll-like receptor (TLR), and NOD-like receptor (NLR) in secreted forms extracellularly present in the bloodstream and interstitial fluids recognize distinct microbial components and directly activate immune cells (Medzhitov and Janeway, 1997; Niles *et al*., 2021; Wicherska-Pawłowska *et al*., 2021; Zhang *et al*., 2022). The activation of these receptors triggers the release of proinflammatory factors, including interferon (IFN), interferon-stimulated gene (ISG), and intracellular inflammatory factors such as IL-6, IL-1β, TNF-α, and IFN. (Zuo *et al*., 2020; Rocchi *et al*., 2022). As a result, infected cells are targeted by a "suicide attack," which inadvertently causes collateral damage to healthy cells and tissue. This damage contributes to increased vascular permeability, disrupted circulation, and increased susceptibility to opportunistic pathogen invasion. Additionally, danger-associated molecular patterns (DAMP) activate the RLR and NLR receptors, further amplifying the production of pro-inflammatory factors (Belančić, 2020; Ngo and Gewirtz, 2021). On the luminal surface of murine intestinal epithelial cells, B°AT1 or SLC6A19, a sodium-dependent neutral amino acid transporter, aids in the formation of tight junction (TJ) that reduces pro-inflammatory cytokine storm

and modulates mucosal cell autophagy via the mechanistic Target of Rapamycin (mTOR) signaling pathway (Fig. 1). However, when a SARS-CoV-2 infection occurs, the ACE-2 and B°AT1 receptor chaperones co-internalize and the total level of B°AT1 on the luminal surface is downregulated, which facilitates the microbiota dysbiosis and enhances the cytokine storm (Wang *et al.*, 2022).

Alteration of Mitochondrial Function in SARS-CoV-2 Infection

The mitochondrial antiviral signaling protein MAVS is an important part of the body's antiviral defense mechanism, which is anchored to the mitochondrial membrane. In contrast, the RLR receptor stimulates MAVS to form oligomers when the SARS-CoV-2 virus enters the cytoplasm. Subsequently, E3 ligase, TNF, tumor necrosis factor receptor–associated factor (TRAF)3, and TRAF6 are among the downstream signaling effectors recruited by MAVS to induce significant amounts of antiviral defense by activating the nuclear factor-κB (NF-κB) pathway (Scott, 2010; Park, 2018; Burtscher *et al.*, 2020). Viruses like the hepatitis C virus, the serine protease NS3/A4, the hepatitis A virus 3ABC protease, and now corona viruses target this pathway by cleaving MAVS and removing it from the mitochondrial outer membrane. This inhibits the pathway and further lowers the cellular capacity of cells to trigger a viral response (Burtscher *et al.*, 2020; Bhowal *et al.*, 2022).

Cells must maintain the precise level of ROS and RNS since they are necessary for signaling (Kaundal *et al.*, 2021). The mitochondria are the major source of cellular ROS, the concentration of which is directly proportional to the activity of the electron transport chain, etc., Alfarouk *et al.*, 2021). A report stated that SARS-CoV-2 triggered COVID-19 hyperinflammation and resulted in mitochondrial redox imbalance (Saleh *et al.*, 2020). The invasion of SARS-CoV-2 infection enhances a series of subsequent events in cells expressing ACE-2 and TMPRSS2. These downstream events activate the NOD-like receptor protein 3 (NLRP-3)-mediated inflammasome signaling pathway, which enhances ROS development, activates the electron transport chain, and increases mt-ROS-a production, resulting in mitochondrial DNA damage (Srinivasan *et al.*, 2021; Chen *et al.*, 2023). Additionally, SARS-CoV-2 infects mitochondria and forms

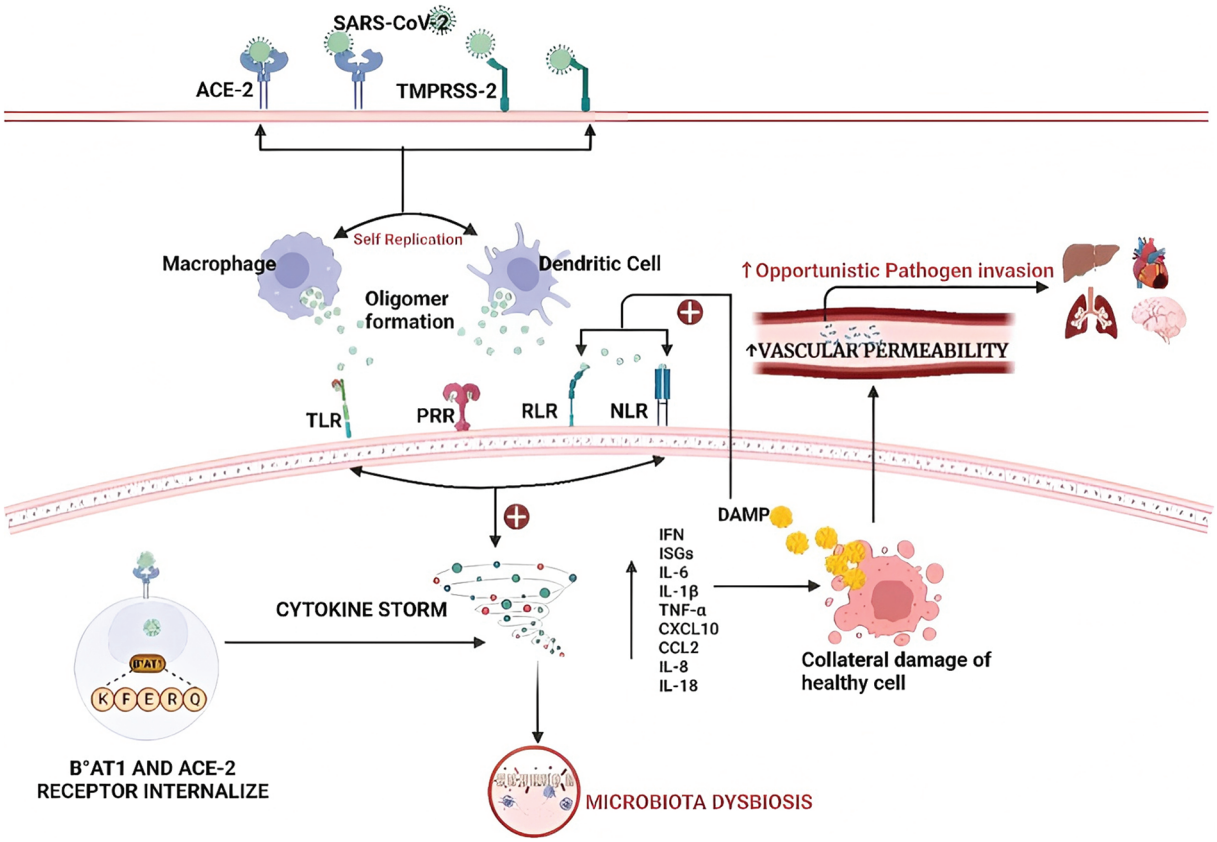

FIGURE 1. Microbiota dysbiosis in the presence of coronavirus: Invasion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via angiotensin-converting enzyme 2 (ACE-2) and type 2 transmembrane protease serine (TMPRSS2) surface receptors present in the epidermal cells. Further, it leads to the formation of oligomers in dendritic cells and macrophages. Further, it activates the RIG-1-like receptor (RLR), Toll-like receptor (TLR), and NOD-like receptor (NLR) resulting in increased production of inflammatory factors that cause the imbalance in microbiota and are responsible for the death of neighboring healthy cells and increased vascular permeability. Abbriviations: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE-2: angiotensin-converting enzyme 2; TMPRSS2: Type 2 transmembrane protease serine; RLR: RIG-1-like receptor; TLR: Toll-like receptor; NLR: NOD-like receptor; B°AT1: Sodium-dependent neutral amino acid transporter; IFN: Interferon; ISG: Interferon-stimulated gene; IL: Interleukin; TNF-α: Tumor necrosis factor α; CXCL: Chemokine (C-X-C motif) ligand; CCL: Chemokine (C-C motif) ligand.

double-membrane vesicles that destabilize the integrity of the mitochondrial membrane. As a result, cardiolipin and mitochondrial DNA are liberated into the cytosol through the mitochondrial membrane, acting as DAMPs. This increases chemokine activity and upregulates the expression of pro-inflammatory genes like TNF-α, IL-6, and TNF-α (Sharma and Sarode, 2022). Subsequently, they switch to a glycolytic metabolism with impaired mitochondria that produce mtROS and further recruit hypoxia-inducible factor-1-α (HIF-1α) (Bhowal *et al*., 2022). This further activates the TLR-9 and NF-κB pathways, increasing the production of inflammatory cytokines (TNF-α, IL-α), which change the dynamics of mitochondria and, ultimately, induce cell death and the progression of COVID-19 disease (Ganji and Reddy, 2021). Additionally, the inflammasome is also formed by the recognition of PAMPs receptors by bacterial toxins, flagellin proteins, muramyl dipeptide, viral or bacterial RNA and DNA, fungal fragments, fungal mannan, zymosan, and protozoa-derived hemozoin. Various classes of patterns recognition receptors (PRRs), including Toll-like receptors (TLR), NOD-like receptors (NLR), C-type lectin receptors (CLR), and Rig-1 Like receptors (RLR) recognize distinct microbial components and directly activate immune cells (Wicherska-Pawłowska *et al*., 2021). The TLR and NLR pathways generate downstream signaling and activate the NF-κB pathway and an inflammatory response to elicit pro-inflammatory cytokines and accelerate mitochondrial ROS production (Li and Chang, 2021). TLR activation also decreases the expression of the uncoupling protein-2 (UCP-2). Further, it increases etc. activity, which further increases mitochondrial ROS production, and stimulation of the TLR pathway. This induces TRAF6 protein that translocates to mitochondria and associates subsequently with ECSIT (evolutionarily conserved signaling intermediate in Toll) (Saint-Georges-Chaumet and Edeas, 2016; Pierelli *et al*., 2017). This protein promotes mitochondrial etc. assembly, accelerates ROS production, and exacerbates inflammation and COVID-19 disease progression (Valdés-Aguayo *et al*., 2021). The mitochondrial dysbiosis in the presence of coronavirus has been illustrated in Fig. 2.

Microbiota-Mitochondria Inter-Talk

The metabolic functions of nutrients are similar in both the microbiome and mitochondria. In addition, they have many structural and functional similarities and several proteins that regulate related or even the same metabolic processes (Fehér *et al*., 2022). According to recent findings, the microbiota interacts with the host cell, particularly by interacting with the mitochondria and microbial metabolites that also affect mitochondrial function and biogenesis (Zhu *et al*., 2022). Further, the mitochondria are responsible for influencing the intestinal functional effector cells, such as immune cells, enterochromaffin cells, and epithelial cells. This, in turn, influences the composition and activity of gut microbiota due to their ability to trigger an innate immune response when bacterial infection or cellular damage is detected (Clark and Mach, 2017). Certain gut microbiota compositions have also been associated with polymorphism of mitochondrial genes, including the *nds* and *cytb* genes or the D-Loop area in the mitochondrial genome (Franco-Obregón and Gilbert, 2017).

The mitochondria can alter the immune response and lead to a rise in inflammation when infected with bacterial or viral pathogens, resulting in microbiota dysbiosis (Saleh *et al*., 2020). In addition, beneficial gut microbiota products, including SCFA, are present in the feces, and secondary bile acid may influence mitochondrial function relating to the production of energy, mitochondria biogenesis, redox balance, and inflammatory cascade (Clark and Mach, 2017). SCFAs (such as butyrate, acetate, and succinate) promote mitochondrial activity and neuroimmune regulation in health and disease. Additionally, SCFA is known to activate the enzyme AMP kinase, which is responsible for mitochondrial genesis (Hu *et al*., 2020; Shandilya *et al*., 2022).

Microbiota- Mitochondria: Therapeutic Biomarkers to Prevent and Treat COVID-19

The gut microbiome plays a key role in immunomodulation. The microbiota may suggest strategies for controlling the gut microbiome to treat, prevent, or at least reduce the impact of COVID-19. These include therapies like fecal microbiota transplantation (FMT), probiotics, prebiotics, and the direct use of bacterial components (Hussain *et al*., 2021).

Probiotics

Probiotics show an immunomodulating function in the cytokine storm—IL-6, IL-1β, IL-15, IL-17 IFN-γ, and TNF-α (Singh and Rao, 2021). The Lactobacillus family of probiotic microorganisms alters the immune response to protect an individual against viral respiratory infections. In order to shield the host from viral respiratory infections, certain strains of lactic bacteria may alter the immune response. The clinical investigator efficacy of *Lactobacillus brevis* CD2 and BLIS K12 in preventing secondary bacterial pneumonia in patients with serious COVID-19 is being evaluated in a Phase II randomized clinical trial (ClinicalTrials.gov Identifier: NCT05175833). Further, the effectiveness of the probiotic *Lactobacillus rhamnosus* GG is being evaluated in a randomized trial which is conducted at Duke University Hospital in preventing COVID-19 transmission and the onset of symptoms in exposed household contacts (ClinicalTrials.gov Identifier No. NCT04399252) (Sundararaman *et al*., 2020; Wang *et al*., 2022). Additionally, some of the randomized controlled trials registered on *ClinicalTrials.gov* investigating the application of probiotics for the prevention/ treatment of COVID-19 are underway or in the recruiting stage (Brahma *et al*., 2022). It has also been reported in clinical studies that oral administration of *L. plantarum* increases cytotoxic CD8 (+) T cells, augments granulocyte-induced phagocytosis, and increases the anti-inflammatory cytokines (IL-4 and IL-10) by reducing the formation of proinflammatory cytokines (IFN-γ and TNF-α) (Nayebi *et al*., 2022). Interestingly, empirical evidence of the antiviral activity of certain probiotic stains against other coronaviruses has already been established. Thus, the advantage of probiotics for

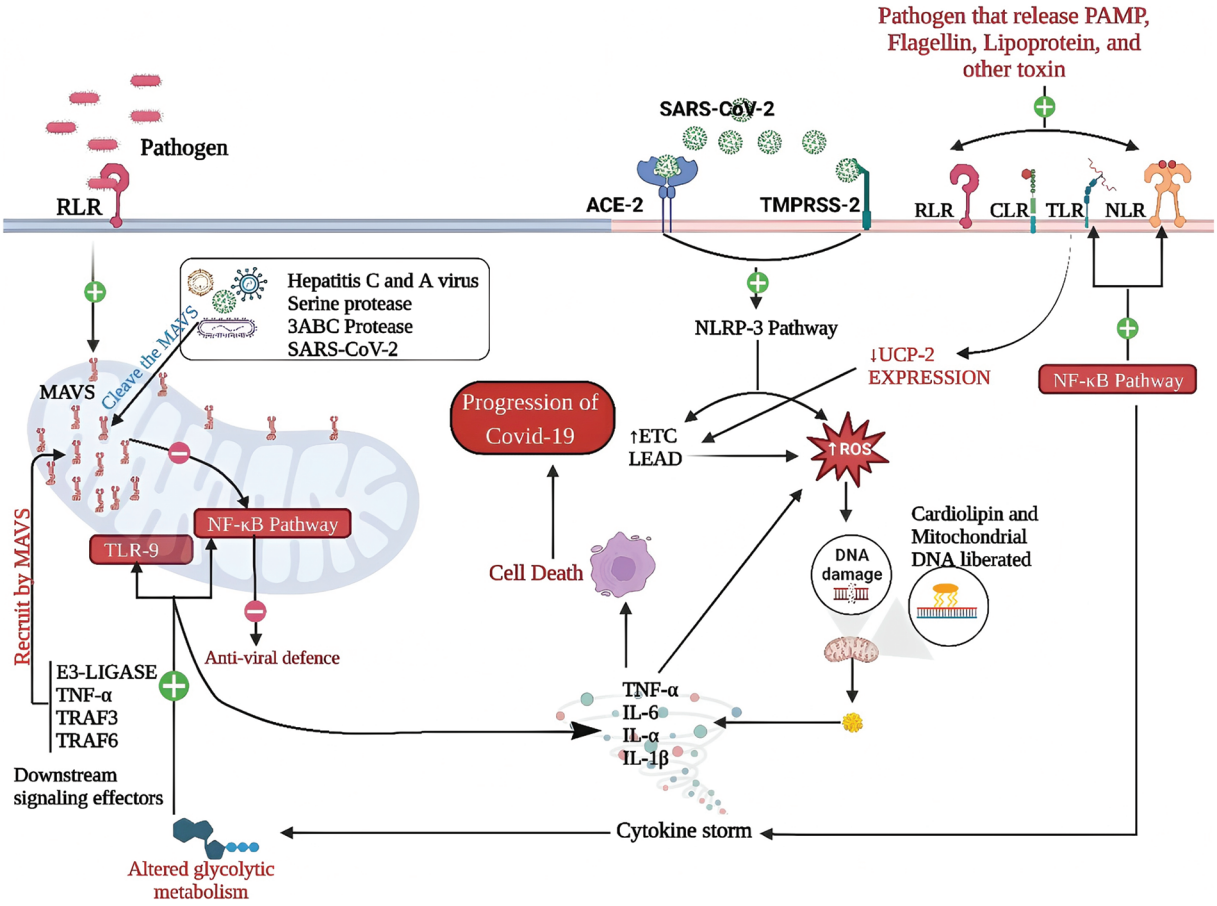

FIGURE 2. Mitochondrial dysbiosis in the presence of coronavirus: The mitochondrial protein MAVS anchors the membrane, defending against viruses. RLR receptor activation prompts MAVS oligomerization. MAVS recruits E3 ligase, TNF, TRAF3, and TRAF6 to activate NF-κB, bolstering antiviral defenses. However, hepatitis C and hepatitis A viruses cleave MAVS, disrupting the response. SARS-CoV-2 infection via ACE-2 and TMPRSS2 activates NLRP-3, causing mitochondrial redox imbalance and DNA damage. Cardiolipin and mitochondrial DNA release into the cytosol act as DAMPs, increasing inflammation. Altered mitochondrial dynamics, elevated mtROS, and TLR/NF-κB activation induce cell death and worsen COVID-19. The recognition of PAMPs by TLRs and NLRs triggers NF-κB, inflammation, and mitochondrial ROS. Decreased UCP-2 and increased, etc. activity worsen mitochondrial ROS, amplifying inflammation and COVID-19 severity.

Abbriviations: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE-2: angiotensin-converting enzyme 2; TMPRSS2: Type 2 transmembrane protease serine; RLR: RIG-1-like receptor; TLR: Toll-like receptor; NLR: NOD-like receptor; IL: Interleukin; TNF-α: Tumor necrosis factor α; TRAF: Tumor necrosis factor receptor–associated factor; NLRP: NOD-like receptor protein; UCP: Uncoupling protein; etc.: Electron transport chain; PAMP: Pathogen associate molecular patterns; ROS: Reactive oxygen speices; MAVS: Mitochondrial antiviral signaling protein; NF-κB: Nuclear factor-κB.

COVID-19 prevention and adjunctive therapy could be considered in the future as mentioned in Table 1 (Santacroce *et al.*, 2021).

Fecal microbiota transplant

Tocilizumab, an anti-IL-6 monoclonal antibody effective in the treatment of arthritis is being studied in clinical trials for patients affected with SARS-CoV-2 (Castelnovo *et al.*, 2021). Several studies demonstrated that post-FMT decreased the number of IL-6 and other inflammatory cytokines. For example, the microbial ecosystem that can produce IL-10 and support the proliferation of regulatory T cells was restored in a patient with inflammatory bowel disease (IBD) receiving FMT (Lopez and Grinspan, 2016; Kazemian *et al.*, 2021). In general, these data support the use of FMT in seriously ill COVID-19 individuals, either as a treatment or an adjuvant to suppress cytokine storms (Nejadghaderi *et al.*, 2021). Recently, research has been conducted to confirm that FMT is effective as an immunomodulatory risk factor for the progression of COVID-19 disease related to increased cytokine storms and inflammation (ClinicalTrials.gov Identifier No. NCT04824222) (Wang *et al.*, 2022).

Prebiotics

Prebiotics are substances found in food that induce beneficial bacteria to grow or function in the gastrointestinal tract (Davani-Davari *et al.*, 2019). Prebiotics may affect COVID-19 by proliferation and survival of probiotic bacteria, enhancing gut diversity of microbial flora and immunity among an adult population (Olaimat *et al.*, 2020). These prebiotics promote the SCFAs-producing microbial gut population, leading to improved inflammatory response and the immune system. This is because the immune responses

TABLE 1

Clinical studies investigating the administration of probiotics and their effects on COVID-19 and related post sequelae

S. No.	Clinical trial	Title	Probiotics/intervention	Outcomes
1	NCT05043376	Study to investigate the treatment benefits of probiotic *Streptococcus salivarius* K12 for mild-to-moderate COVID-19	*Streptococcus salivarius* K12	Clinical improvements were observed in patients
2	NCT04937556	Evaluation of probiotic supplementation in the immune response of participants with COVID-19 (coronavirus disease)	*Lactobacillus salivarius*	Conc. of specific antibodies proportional to the SARS-CoV-2 virus
3	NCT04907877	Bifido- and Lactobacilli in symptomatic adult COVID-19 outpatients (ProCOVID)	A mixture of bifido- and lactobacteria	Global symptom score
4	NCT04877704	Symprove (probiotic) as an add-on to COVID-19 management	Multi-strain probiotic	Duration of hospitalization
5	NCT04854941	Efficacy of probiotics in the treatment of hospitalized patients with novel coronavirus infection	*Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum Subsp. infantis* & *Bifidobacterium longum*	Mortality of patients during hospitalization
6	NCT04756466	Effect of the consumption of a Lactobacillus strain on the incidence of COVID-19 in the elderly	Lactobacillus	Incidence of infection by PCR or antigen test

are known to be controlled by SCFAs (Markowiak-Kopeć and Śliżewska, 2020). It is well documented that SCFAs, particularly butyrate can strengthen the gut barrier function and thus reduce the inflammatory response. Compared to FMT, treatment with prebiotics and probiotics is safer and more effective in terms of their preparation and administration (Cristofori *et al*., 2021).

Characterization of COVID-19 microbiota in the airway plays an important role in developing strategies for the management of the pathogenesis of COVID-19 (Liu *et al*., 2022b). Physicians recommend probiotics or prebiotics to restore the gut flora, which act as anti-inflammatory immunomodulators to improve mitochondrial health. Useful therapeutic strategies can be used to specifically target to improve mitochondrial health or reduce the generation of ROS, which was increased during the impaired mitochondrial metabolic pathways. The circulating cell-free mitochondria in human blood are an intriguing novel pathway with promising potential as a biomarker, therapy target, and therapeutic agent (Olaimat *et al*., 2020; Stier, 2021).

Conclusion

The interplay between the microbiota and mitochondria has been recognized as an important factor in various physiological processes, including the immune system and its responses. In the context of COVID-19, it has been suggested that dysregulation of this interplay may contribute to disease severity. Recent research has shown that changes in the gut microbiota may be linked to mitochondrial dysfunction, which could potentially contribute to COVID-19 pathogenesis. Additionally, mitochondrial dysfunction has been implicated in developing acute respiratory distress syndrome (ARDS), a common complication of severe COVID-19. Therapeutic biomarkers and interventional approaches targeting the microbiota-mitochondria axis may offer potential strategies for treating COVID-19. For example, probiotics and prebiotics have been presented to have a beneficial effect on the gut microbiota and may therefore help to mitigate COVID-19-associated dysbiosis. In addition, interventions aimed at improving mitochondrial function, such as using mitochondrial-targeted antioxidants, may also be beneficial in treating COVID-19. In conclusion, the microbiota-mitochondria interplay plays a crucial role in COVID-19 pathogenesis. However, further research is needed to understand the mechanisms underlying this relationship completely and to develop targeted therapeutic interventions that can improve patient outcomes. To summarize, the potential of microbiota and mitochondrial-targeted interventions offers promising avenues for managing COVID-19.

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