Melatonin Protects Mitochondria and Adenosine Triphosphate Production

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Melatonin (N-acetyl-5-methoxytryptamine) is a ubiquitous, mitochondria-targeted molecule present in all tested eukarya and bacteria. In March 2022, the first discovery of the serotonin N-acetyltransferase (*SNAT*) gene—responsible for the penultimate formation of N-acetylserotonin (NAS) before its final conversion into melatonin — in archaea further consolidates the status of melatonin as a regulator of biomolecular condensates in all three domains of life in the cellular empire. RNA viruses including SARS-CoV-2 contain proteins with intrinsically disordered regions that undergo liquid-liquid phase separation (LLPS). Liquid-liquid phase separation (LLPS) of these proteins form membraneless condensates that act as “viral factories” to facilitate and enhance replication. Phase separation of the SARS-CoV-2 nucleocapsid (N) protein is associated with mitochondrial dysfunction and rewiring of energy production away from oxidative phosphorylation (OXPHOS) to favor aerobic glycolysis in cytoplasm. Increased adenosine triphosphate (ATP) in cytoplasm supports viral replication. Melatonin protects mitochondria from damage, maintains adequate levels to disassemble “viral factories”, and prevents suppression of host antiviral immune responses by inhibiting nucleocapsid phase separation via antioxidant-dependent and -independent means.

melatonin Mitochondria ATP

1. Introduction

Mitochondria are the “energy powerhouse of the cell” that control respiration and ATP synthesis [1][2], and mitochondria are directly targeted by viruses during infection to facilitate the modulation of cellular metabolism and innate immunity [3]. The fundamental features of optimal mitochondrial dynamics are characterized by the ability to connect and elongate (fusion), divide (fission), and turnover (mitophagy). Disruption of mitochondrial bioenergetics during viral infections may explain how RNA viruses hijack mitochondrial dynamics to support viral replication and persistence [4]. Both the hepatitis B and hepatitis C viruses promote chronic liver damage by altering the balance of mitochondrial dynamics towards fission and mitophagy in order to reduce virus-induced apoptosis, thereby enhancing viral persistence [5][6]. The SARS-CoV-2 virus relies on a sophisticated, multipronged approach to commandeer and manipulate mitochondrial dynamics and metabolism, evading mitochondria-dependent immune response to promote viral replication and pathogenesis [7]. The SARS-CoV-2 dsRNA, which is an intermediate of positive-strand RNA virus replication, has been found to localize in mitochondria [8], while computational modeling of SARS-CoV-2 viral RNA subcellular localization revealed much stronger transcript residency signals toward the mitochondrial matrix and nuclear compartments compared to other coronaviruses [9]. An analysis of changes in

molecular composition of mitochondria captured by Raman microspectrometry and biomolecular component analysis (BCA) algorithm found a marked reduction in mtDNA content in microglia treated with spike protein or heat-inactivated SARS-CoV-2 virus [10].

Integrative imaging techniques provided evidence of extensive alterations to cellular organelles, including significant fragmentation of the Golgi apparatus and perturbation of mitochondrial morphology and function. Mitochondria in cells infected by SARS-CoV-2 displayed swollen cristae and matrix condensation, together with significant decreases in mitochondrial adenosine triphosphate (ATP) synthase subunit 5B (ATP5B) that implies metabolic rewiring away from oxidative phosphorylation in favor of glycolysis [11][12]. The SARS-CoV-2 virus enhances replication by causing mitochondrial dysfunction via membrane depolarization and mitochondrial permeability transition pore (mPTP) opening in a time-dependent manner, with more damage observed at 12 h post-infection compared to 3 h. In order to prevent clearance and degradation of damaged mitochondria, the SARS-CoV-2 virus stalls initiated mitophagy to suppress mitochondrial quality control and clearance of virus by inhibiting binding of mitophagy mediator LC3 and its binding adaptor protein p62 [8][13]. In diabetic cardiomyopathy (DCM), the clearance of dysfunctional mitochondria by mitophagy is often impaired. In a DCM mouse model, melatonin supplementation at 20 mg/kg/day for 4 weeks increased the expression of both LC3-II and p62, resulting in upregulated Parkin-mitophagy that increased clearance of dysfunctional mitochondria to restore mitochondrial quality control [14].

2. Melatonin Rescues Mitochondrial Membrane Potential from SARS-CoV-2 Envelope Protein-Induced Depolarization

RNA viruses and bacterial infections promote ion channel activities, resulting in membrane depolarization that can activate pro-inflammatory, apoptotic NLR pyrin domain containing 3 (NLRP3) inflammasomes that are a major source of inflammatory IL-1β and IL-18 cytokines [15][16][17][18]. The SARS-CoV envelope (E) protein is a viroporin that regulates host cell microenvironment including pH and ion concentrations, causing death in humans and animal models by inducing the pro-inflammatory NLRP3 inflammasome response [19][20][21]. Using similar mechanisms, the SARS-CoV-2 E protein also increases pathogenicity by forming a homopentameric cation channel to modify host ion channel homeostasis in support of viral replication [22][23][24][25]. Mutations of the E protein can enhance the open channel conformation in ion-channel functionality, causing increased virulence and pathogenicity that are correlated with high COVID-19 mortalities [26]. Ion channels formed by viroporins not only allow water and ions to penetrate cell membranes [27], but also generate progressive membrane permeation and damage, disrupting membrane potential and collapsing ionic gradients that facilitate viral budding and release, spreading the virus to surrounding cells [28][29]. Molecular dynamic simulations demonstrated that the E protein can promote viral replication by reducing intracellular calcium in transfected cells and enhance viral budding by bending surrounding lipid bilayers [30].

2.1. Membrane Depolarization Impairs Oxidative Phosphorylation and Cation Homeostasis

Mitochondria infected by SARS-CoV-2 display swollen cristae [11][31][32]. Modulations to cristae topology directly affects mitochondrial function and bioenergetics [33]. ATP synthesis during oxidative phosphorylation (OXPHOS) in mitochondria is dependent upon the F_1F_0 ATP synthase (complex V) of the electron transport chain (ETC) to drive proton re-entry powered by chemical energy maintained by the negative membrane potential (ΔΨm) of inner mitochondrial membrane (IMM) consisting of inner boundary membranes (IBMs) and cristae—the principal site of oxidative phosphorylation in mitochondria [34][35][36][37]. Changes in the ΔΨm—depolarization or hyperpolarization—by a decrease (less negative) or an increase (more negative) of the ΔΨm, respectively, can alter mitochondrial homeostasis and bioenergetics [34]. Proper ΔΨm of IBM maintains a strong electrical force to keep protons close to cristae membrane within the intercristal space (ICS; cristae lumen) [38][39][40]. Depolarization of the mitochondria membrane can cause a partial or complete collapse of the ΔΨm [41], resulting in dysfunctional, swollen, unfolded cristae that no longer can maintain optimal ATP production via OXPHOS [42]. Decline of the ΔΨm causes matrix condensation, leading to the unfolding of cristae which expands matrix volume to cause mitochondrial swelling [43][44]. Decreased ΔΨm reduces ATP production by lowering ETC activities, but targets damaged areas for clearance by mitophagy [45][46][47]. Yet, inhibition of mitophagy by SARS-CoV-2 prevents the timely clearance of dysfunctional mitochondria that prevents higher ATP production via OXPHOS in favor of glycolysis [12][48][49][50].

Membrane depolarization from viroporin ion channel activities can elevate production of reactive oxygen species (ROS) via increased matrix pH due to cation influx and/or anion efflux [51]. Depolarization opens different types of voltage-gated calcium channels (VGCCs) in a wide range of cell types including both excitable and nonexcitable cells [52][53]. Opening of VGCCs allows the rapid influx of extracellular calcium (Ca^{2+}) that serves as electrical signaling messengers to initiate different important cellular processes [54]. Viruses—including the poliovirus [55], alphavirus [56], human immunodeficiency virus type I (HIV-1) [57], influenza virus [58], SARS-CoV [59], and SARS-CoV-2 [22]—encode viroporins to form ion channels in host cell membranes that facilitate membrane permeability to promote viral entry, replication, release, and dissemination to surrounding cells [59]. Dysregulated calcium signaling may underlie autonomic dysfunctions [60][61] often associated with post-acute sequelae of COVID-19 (PASC) [62][63][64], including postural orthostatic tachycardia syndrome (POTS) [65][66]. Unlike viroporins of other viruses that increase intracellular Ca^{2+} by modulating plasma membrane permeability [67][68], the SARS-CoV-2 E protein can decrease Ca^{2+} content in transfected cells by ~61.5% (0.1286 ± 0.0745 AU, N = 22) compared to nontransfected cells (0.2002 ± 0.096, N = 19; $p = 0.01$), indicating potential leakage, suppression, or sequestration of Ca^{2+} by the virus. Secondary osteoporosis often occurs with PASC, where a decrease in bone mineral density (BMD) by a mean of 8.6% (± 10.5%) could be detected in COVID-19 at a mean of 81 (± 48) days after hospital discharge. This significant loss in BMD far exceeded normal age-related annual BMD loss, resulting in a two-fold increase in the osteoporosis ratio [69].

Furthermore, the SARS-CoV-2 E protein is localized intracellularly and may be responsible for proton efflux in transfected cells [30]. An acidic pH can adjust the conductivity and ion selectivity of the ion-conducting transmembrane domain of E protein by protonating the Glu8 side chain carboxyl, altering the carboxy-terminal conformation [24]. The influenza B virus viroporin proton channel is pH-gated and mediates virus uncoating when activated by acidic pH [70]. Ionic imbalances in cells affecting the homeostasis of cations, including calcium (Ca^{2+}),

magnesium (Mg^{2+}), zinc (Zn^{2+}), potassium (K^+), and sodium (Na^+), can interfere with innate and adaptive immunity that affect the pathogenicity of viruses [19][71][72][73].

2.2. Viroporin Ion Channel Activities May Regulate Virus Phase Separation

Potassium (K^+) efflux triggers the activation of the NLRP3 inflammasome upon infection by RNA viruses [15], including SARS-CoV-2 [74][75], where elevated urinary loss of potassium is often associated with COVID-19 disease severity [76]. Experimental work showed the SARS-CoV-2 ORF3a viroporin priming and activation of the NLRP3 inflammasome were dependent upon K^+ efflux [77]. K^+ is a rate-liming modulator of the glutamate transport cycle, where intracellular K^+ relocates the glutamate binding site to the extracellular side of the membrane, and extracellular K^+ induces glutamate release upon transporter relocation [78]. Glutamate promotes LLPS of the *Escherichia coli* single-stranded-DNA binding protein [79]. Thus, K^+ efflux that can elevate glutamate availability [80] may enhance SARS-CoV-2 phase separation. Indeed, altered glutamine metabolism and dependence on glutamine receptor subtype 2 for internalization are associated with SARS-CoV-2 infections [81][82]. Mitochondrial dynamics dysfunction and Ca^{2+} dysregulation as a result of membrane depolarization induced by viroporin ion channel activities can also affect leucocyte functionality to suppress and evade immune responses during SARS-CoV-2 infection to enhance viral phase separation for viral replication.

3. Melatonin Attenuates Membrane Depolarization and Balances Ion Homeostasis by Antioxidant-Dependent and -Independent Mechanisms to Protect Mitochondria and Lymphocytes during Viral Infection and PASC

Leukocytes of patients recovered from COVID-19 presented loss of mitochondria membrane potential (ΔΨm) even at 11 months post-infection [83]. Leukocytes are responsible for the production of first line IFN-α immune response [84][85], and the loss of ΔΨm caused by viroporin-mediated membrane depolarization may be one of the most important underlying causes for the development of PASC [83]. Lymphopenia and the depletion of T lymphocyte subsets were found in 98% (153/157) of patients infected by SARS-CoV in 2003 without any preexisting hematological disorders [86]. Correspondingly, patients infected by SARS-CoV-2 are associated with persistent lymphopenia [87][88] and functional exhaustion of lymphocytes [89]. COVID-19 disease progression is correlated with a nearly three-fold increased risk of severe COVID-19 (random effects model, OR = 2.99, 95% CI: 1.31–6.82) [90], while low lymphocyte counts in patients are deemed to be effective predictors of disease severity and hospitalization [91][92].

T lymphocytes are dependent upon functional mitochondria to supply local ATP and to maintain Ca^{2+} homeostasis and signaling during all stages of immune response [93][94]. In T lymphocytes, expression of 75% of the genes associated with survival and proliferation are dependent upon Ca^{2+} influx [95], while mitochondrial dynamics often affect T lymphocyte chemotaxis, where mitochondrial fusion protein OPA1 inhibits lymphocyte migration and chemotaxis, but fission enhances both migration and chemotaxis [96]. It is perhaps not a coincidence that depolarization of mitochondrial membranes can activate dynamin-related GTPase OPA1-dependent fusion to

inhibit lymphocyte chemotaxis [97], and that the E protein viroporin can deplete intracellular Ca^{2+} content [30]. Stimulation of T lymphocytes triggers immediate accumulation of active mitochondria with elevated Ca^{2+} influx and heightened OXPHOS, which can also cause transient collapse of ΔΨm due to intense ETC activities, ion flux, and ATP release across the mitochondrial membrane [93]. Thus, inability to repolarize ΔΨm results in a reduction of ATP generation from the loss of electrochemical potential that maintains the gradient that drives the F_1F_0 ATP synthase (complex V) [45][98]. Moreover, membrane depolarization also prevents store-operated Ca^{2+} influx after store depletion [99]. Cell sorting experiments revealed that mtDNA damage occurs only in human fibroblast cells with low ΔΨm sustained for 24 h. These cells exhibited continuous, elevated production of hydrogen peroxide (H_2O_2) that potentially accentuated a feed-forward cascade of increasing ROS that impaired repair responses and increased mtDNA lesions, resulting in apoptosis [100]. Taken together, membrane depolarization by E protein suppresses not only ATP-dependent purinergic signaling that supports T lymphocyte immune response functions, but also T lymphocyte-mediated expression of genes that are dependent upon Ca^{2+} influx [93][95]. In its multipronged strategies against the SARS-CoV-2 virus, melatonin not only promotes the production of leukocytes [101], but also attenuates membrane depolarization to protect lymphocyte functionality (**Figure 1**).

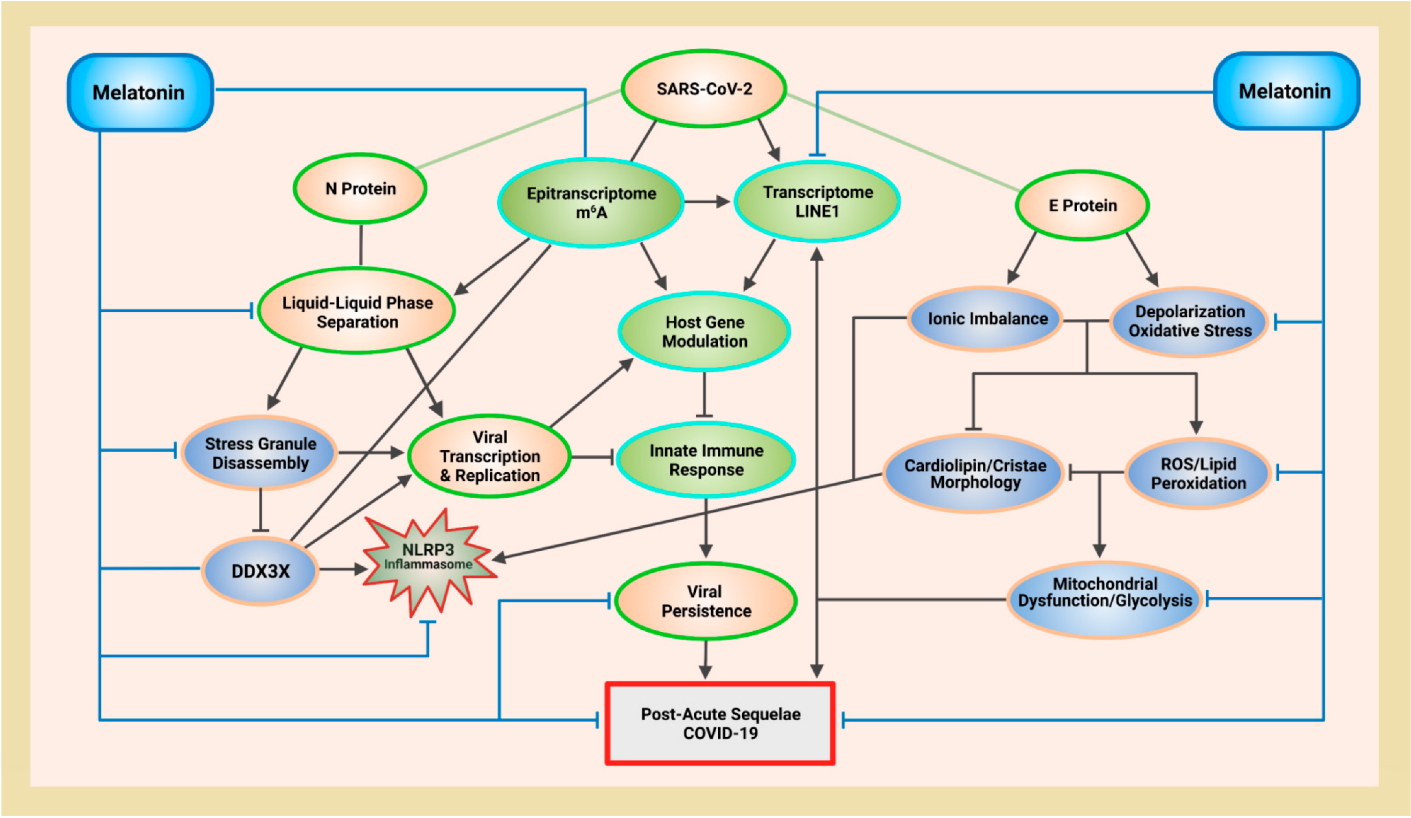

Figure 1. Schematic illustrating melatonin attenuation of acute infection, viral persistence, and post-acute sequelae COVID-19 (PASC) from potential alterations to the epitranscriptome and transcriptome via RNA m^6A modifications and LINE1 derepression by the SARS-CoV-2 virus. The envelope (E) protein causes extensive mitochondrial distress and elevates oxidative stress via membrane depolarization and ionic imbalances that activate LINE1 derepression, NLRP3 inflammasome apoptotic signaling, stress granule formation, and nucleocapsid (N) protein liquid-liquid phase separation (LLPS). N protein LLPS forms membraneless condensates that not only facilitate

viral transcription, genome packaging, and dissemination, but also enhance the suppression of host gene expression to evade innate immune responses via the disassembly of stress granules and the hijacking of DEAD-box RNA helicase DDX3X. Melatonin employs antioxidant-dependent and -independent strategies to modulate m^6A modifications, suppress LINE1 derepression, rescue mitochondrial dysfunctions, and reduce oxidative stress. Melatonin regulates N protein LLPS to block the sequestration of DDX3X and the formation of NLRP3 inflammasome, as well as the disassembly of stress granules to support innate antiviral immune response, inhibiting viral transcription and replication, maintaining host gene stability and integrity to prevent severe disease and PASC (see Abbreviations for additional acronyms).

Melatonin is a pleiotropic molecule that can maintain optimal membrane potential by either increasing or reducing ΔΨm for maximum efficiency. In hyperpolarized, prorenin-treated microglia, treatment with 100 μM melatonin reduced ΔΨm and attenuated hyperpolarization and ROS overproduction [102]. Conversely, in mitochondria of human oocytes, 10 μM melatonin treatment decreased excessive intracellular Ca^{2+} levels to restore mitochondrial function and significantly increased membrane potential compared to control levels [103], while 1 μM melatonin added to post-thawed equine sperm increased mitochondrial membrane potential and improved mitochondrial function [104]. Membrane depolarization prevents store-operated Ca^{2+} influx after store depletion [99], disrupting T lymphocyte-mediated gene expressions [95]. However, treatment with 500 μM melatonin markedly elevated cytosolic calcium in human platelets by evoking store-operated calcium release from platelet mitochondria [105]. An analysis of human neutrophil respiratory burst and membrane potential changes found melatonin to increase depolarization at concentrations up to 0.5 mM, whereas 2 mM melatonin concentration decreased ΔΨm in neutrophils activated by phorbol 12-myristate 13-acetate (PMA) [106]. Mitochondrial inner membrane depolarization in human HaCaT keratinocytes irradiated with UVB radiation (50 mJ/cm^2) was normalized by preincubation with 0.01 mM to 1 mM melatonin via the reduction of mitochondrial ROS (mROS) and inhibition of mitochondrial permeability transition pore (mPTP) opening [107].

Viroporin-induced membrane depolarization elevates production of ROS via ionic imbalances from dysregulated cation influx and/or anion efflux [51]. The SARS-CoV-2 virus can also escalate ROS release in Vero E6 cells via opening the mPTP, causing subsequent depolarization and further oxidative stress damage in a time-dependent manner [8][108]. In a self-perpetuating positive feedback loop, oxidative stress from unneutralized excess ROS leads to even more rapid depolarization of the inner mitochondrial membrane potential and subsequent disruption of OXPHOS and ATP production. Damaged mitochondria continue to produce more ROS, resulting in the dreaded ROS-induced ROS release (RIRR) loop [109]. ROS can also cause physiological lipid peroxidation [110], where oxidants attack the carbon-carbon double bond in lipids, initiating a cascading chain reaction that terminates in the formation of reactive aldehyde end products including 4-hydroxynonenal (HNE) [111]. In a pilot study of 21 critically ill COVID-19 patients admitted to the ICU, the only difference in clinical or laboratory parameters monitored between the 14 patients who recovered and the 7 who passed away was the significantly higher level of HNE-protein adducts ($p < 0.05$) obtained from the plasma of the deceased patients compared to levels in survivors during the initial 1–3 days in hospital [112].

Melatonin and its metabolites are potent inhibitors of lipid peroxidation cascades and are extremely effective at scavenging different types of ROS [113][114][115][116][117][118][119]. In leukocytes irradiated with 750 mJ/cm^2 UVB light (280–360 nm, max: 310 nm), treatment with melatonin suppressed ROS directly in a dose-dependent manner where 10 mM melatonin reduced ROS formation in leukocytes by 260-fold, while 7.5 mM and 5 mM reduced ROS by 120- and 60-fold, respectively [120]. In addition to decreasing ROS via antioxidant-dependent mechanisms [121][122], the regulation of depolarization by melatonin may be via an ionic-based, antioxidant-independent mechanism. The repolarization of gonadotrophin-releasing hormone (GnRH)-induced membrane depolarization in neonatal rat pituitary cells by melatonin could be mediated through the inhibition of Ca^{2+} influx or a hyperpolarization mechanism that is sodium-dependent, involving modulation of the Na^+/K^+-dependent ATPase [123]. Jurkat cells undergo apoptosis from anti-Fas-induced mitochondrial membrane depolarization where inhibition of the Na^+/K^+ ATPase prevented membrane repolarization via the suppression of monovalent ion movements, particularly the intracellular accumulation of Na^+ during sustained depolarization without repolarization [124].

Melatonin is an osmoregulator with pleiotropic effects on plasma sodium concentration in animal models [125][126]. This ancient molecule is indispensable in maintaining ion homeostasis in plants [127][128][129], and its comprehensive role as a “broad-based metabolic buffer” includes rhythmic circadian modulation of the Na^+/K^+-ATPase as well as the Na^+/H^+ exchanger ion-transport activities in human erythrocytes via antioxidant-dependent and -independent mechanisms [130][131]. Both Na^+/K^+-ATPase and Na^+/H^+ can influence transmembrane chemical gradients [132][133], as well as cytosolic pH and ionic balance [134][135][136]. Therefore, it is not inconceivable that melatonin can adjust salt homeostasis via Na^+/K^+-ATPase to regulate LLPS during viral infections as high salt or extremely low salt concentration can inhibit LLPS [137]. Hyponatremia where plasma sodium concentration is below 135 mmol/L is often associated with viral infections including COVID-19 [138]. Furthermore, in vitro experiments found 1.5% NaCl solution can achieve 100% inhibition of SARS-CoV-2 replication in nonhuman primate kidney Vero cells, while 1.1% of NaCl can inhibit viral replication by 88% in human epithelia lung Calu-3 cells [139].

The Na^+/K^+-ATPase is a P-type ATPase that utilizes energy from ATP hydrolysis to pump ions across membranes generating an electrochemical gradient [140]. Nonmitochondrial ATPases including P-type Na^+/K^+-ATPases are often localized in lipid raft microdomains in lipid bilayers of plasma membranes [141][142][143]. Increased ROS from oxidative stress can reduce membrane fluidity and performance of Na^+/K^+-ATPases [144][145][146][147]. Melatonin maintains membrane fluidity by inhibiting lipid peroxidation cascades in an antioxidant-dependent manner [114][115][148][149][150], while its ability to stabilize liquid-ordered (L_o)-liquid-disordered (L_d) phase separation in lipid bilayers (tested over a range of temperatures up to 45 °C) preserves necessary lipid raft composition and nanoscopic structure to support various ATPase activities, including those of Na^+/K^+-ATPases [130][151].

An analysis of information obtained from various neutron scattering techniques accessing membrane structure and dynamics from SARS-CoV-2 protein–host interactions revealed that molecular interactions during spike protein fusion peptide binding events could induce changes in membrane fluidity and rigidity where fusion peptide 1 increased rigidity while fusion peptide 2 reduced fluidity [152]. Other morphological changes induced by SARS-CoV-2 as a result of fusion events include modification of both lipid composition and membrane structure to produce non-lamellar cubic membranes that facilitate membrane fusion during viral infection [153]. The oxidation of high

curvature lipids such as cardiolipin (CL) can result in the rearrangement of lipids in plasma membranes from a fluid lamellar phase to a non-lamellar cubic phase that can impact membrane integrity and stability. The fact that cubic membranes are usually found in membranes with high intrinsic curvature, such as mitochondrial inner membranes with deep cristae invaginations formed by high-curvature lipids that host ATP synthase dimers [154][155][156], further explains how SARS-CoV-2 and other viruses modulate mitochondrial function to favor glycolysis over OXPHOS.

4. Melatonin Protects Mitochondria Cristae Morphology and ATP Production via Antioxidant-Dependent and -Independent Mechanisms

Phase separation of SARS-CoV-2 N protein may be biphasically modulated by ATP where ATP can completely dissolve viral condensates, which promote pathogenicity and replication, formed by N protein LLPS at molar ratios of 1:500 (N-protein:ATP), but enhance assembly of condensates from low molar ratios of 1:25 up to 1:200 [157]. Hence, mechanisms associated with viral fusion and enhanced viral replication involve targeting of mitochondrial bioenergetics and the production of ATP. An analysis of bulk RNA-seq datasets from COVID-19 patients and healthy controls revealed a marked reduction of mtDNA gene expression in various types of cells including the immune system, with concomitant elevation of genes expressing glycolytic enzymes, and ROS production [48], while an interactome analysis identified multiple mitochondrial proteins that interact with the SARS-CoV-2 N protein [158]. Elevated glucose and sustained aerobic glycolysis in monocytes of COVID-19 patients are directly responsible for boosting viral replication, causing increased NLRP3 inflammasome and cytokine production, inhibition of T proliferation, and apoptosis of lung epithelial cells [50][159]. Metabolic alterations in live peripheral blood mononuclear cells (PBMC) obtained from patients with COVID-19 showed extensive mitochondrial dysfunction with compromised respiration but increased utilization of glucose serving as primary substrate for energy production in place of OXPHOS [160]. Substituting OXPHOS ATP production with aerobic glycolysis may lead to a more than 16-fold reduction of ATP. The theoretical maximum of ATP calculated from simultaneous measurements of oxygen consumption and extracellular acidification showed OXPHOS to yield 31.45 ATP/glucose (maximum total yield 33.45), whereas glucose yields only 2 ATP/glucose [161]. Considering ATP can completely dissolve N protein phase separation condensates at concentrations 2.5- to 20-fold above assembly concentrations, with disassembly starting beyond 8-fold increases, it is not surprising that the timely application of melatonin can effectively suppress viral replications.

4.1. Melatonin Suppresses Aerobic Glycolysis to Enhance Oxidative Phosphorylation

Melatonin is a powerful glycolytic that can inhibit aerobic glycolysis (the “Warburg effect”) by steering pyruvate metabolism towards the citric acid (tricarboxylic acid, Krebs) cycle and OXPHOS, and avoiding aerobic fermentation of glucose by glycolysis [162][163][164]. Melatonin can enhance mitochondrial OXPHOS ATP production [165] by different mechanisms including the stimulation of the SIRT3/PDH axis to reverse the Warburg phenotype in lung cancer cells in vitro [166]; and the suppression of hexokinase-2 overexpression to ameliorate glycolytic overload, improving mitochondrial ATP production and normalizing glycolysis to protect mitochondrial function in

chronic kidney disease mesenchymal stem/stromal cells [167]. The SARS-CoV E protein ion channel induces membrane permeabilization that decreases ΔΨm in mitochondrial inner membranes [27][83]. Loss of membrane potential not only reduces ATP production due to impaired OXPHOS, but can induce the production of even more ROS due to accumulation of reducing equivalents from lower ETC activities that result in the creation of reductive stress that continues generate additional ROS to perpetuate the RIRR positive feedback loop [34][109][168][169]. The generation of excess ROS during SARS-CoV-2 infection [8] can initiate powerful lipid peroxidation cascades that damage lipid composition of the cristae, resulting in loss of ATP synthase function.

4.2. Melatonin and Metabolites Preserve Cardiolipin Function in Cristae by Preventing Lipid Peroxidation Cascades

The apex of deep IMM cristae invaginations provides the ideal location for hosting dimerized ATP synthases of eukaryotic mitochondria [154][170]. Dimerized ATP synthases are seven-fold more active than ATP monomers [171], and dimerization of ATP synthases is a prerequisite for shaping the high curvature cristae structure [172][173]. The deep negative membrane curvatures at the apexes of cristae are maintained by the unique cone-shaped structure of cardiolipin (CL) that not only increases bending elasticity of the IMM but also the regulation of formation and stability of respiratory chain complexes [174][175][176][177]. Accordingly, mitochondrial membranes can comprise up to 25% CL [178][179]. CL is a negatively charged, dianonic lipid that can dramatically lower pH at membrane interfaces to increase proton (H^+) concentration (~700 to ~800) [180][181] to elevate ATP production [182]. The oxidation of just one fatty acid chain in CL can lead to vast conformational changes in the entire molecule, resulting in reduced membrane thickness, and potential impairment of proton and electron transport that are dependent on CL-mitochondrial protein interactions [183][184]. Elevation of ROS as a result of depolarized mitochondrial membranes during viral infection may increase peroxidation of cardiolipin. The destabilization of mitochondrial supercomplexes as a result of CL peroxidation affects mitochondrial bioenergetics, leading to impaired OXPHOS, reduced ATP production, and other mitochondrial dysfunctions in different tissues manifested in a range of pathophysiological conditions including heart ischemia/reperfusion, heart failure, diabetes, and Barth syndrome [185][186][187][188][189][190][191]. In *Saccharomyces cerevisiae*, disruption of the CRD1 gene responsible for encoding CL synthase resulting in the absence of CL in mitochondria membranes led to a loss of mitochondrial ΔΨm and mitochondrial genome when cultured at prolonged elevated temperature of 37 °C [192]. Interestingly, circulating anticardiolipin antibodies (aCL), which may cause endothelial dysfunction and elevated IgA-aCL, is often associated with increased ischemic burden in patients with coronary artery disease (CAD) [193].

Critically ill COVID-19 patients with coagulopathy and thrombocytopenia often manifest the presence of anticardiolipin antibodies in serum [194]. A meta-analysis and systematic review of 21 studies with 1159 hospitalized COVID-19 patients discovered the presence of antiphospholipid antibodies in ~50% of the patients. Severe disease was correlated with a higher prevalence of aCL (IgM or IgG) compared to noncritical disease (28.8% vs. 7.10%, $p < 0.0001$) [195]. Oxidized LDL bound by anti-lipoprotein antibodies are correlated with IgG-aCL and IgM-aCL [196]; thus, the presence of elevated aCL and other antiphospholipid antibodies is indicative of systemic lipid peroxidation, which may then explain the development of thromboses in the absence of correlated D dimer levels in about one-third of severely ill COVID-19 patients [193][197]. In fact, elevated lipid peroxidation is the only oxidative

stress biomarker that is significantly different between intubated COVID-19 patients and/or those who died compared to patients with mild disease. In addition, patients whose lipid peroxidation rose above 1948.17 μM were either intubated or died 8.4 days earlier on average (mean survival time 15.4 vs. 23.8 days) [198]. Melatonin is a potent antioxidant that can protect mitochondrial function by neutralizing ROS to inhibit CL peroxidation [199]. The addition of 10 μM melatonin to rat heart mitochondria almost entirely prevented membrane depolarization induced by Ca^{2+}/tert-Butylhydroperoxide (t-BuOOH), a peroxidation promoting peroxide, in addition to reversing cytochrome c release, and mitochondrial matrix swelling [116]. The reason why melatonin is uniquely suited to prevent lipid peroxidation cascades is in large part due to its preferential localization at hydrophilic/hydrophobic membrane interfaces.

Melatonin is uncharged in the entire pH range [200]. Even though melatonin is nonpolar, it can form strong H-bonds with hydrophilic lipid headgroups at hydrophilic/hydrophobic membrane interfaces [201]. Thus, melatonin becomes an efficient scavenger of both aqueous and lipophilic free radicals as a result of the presence of both hydrophilic and lipophilic moieties in the melatonin molecule [202]. As such, melatonin and its metabolites easily neutralize both the hydroxyl radical (•OH) and the hydroperoxyl radical (•OOH) [203][204]—two dominant ROS molecules that can initiate and sustain chain oxidation reactions of unsaturated phospholipids including CL in plasma membranes [205][206] and mitochondria [207][208]. During viral infections, ionic imbalances from viroporin ion channel activities activate the pro-inflammatory NLRP3 inflammasome which mediates the production of cytokines that can contribute to severe pathophysiology and disease [17][209]. Heightened expression of the NLRP3 inflammasome was detected in leukocytes in the lungs of all patients who did not survive COVID-19 [210]. Melatonin targets NLRP3 inflammasome-mediated cytokine release employing antioxidant-dependent and -independent mechanisms [211].

5. Melatonin Targets NLRP3 Inflammasomes via Cardiolipin and DDX3X

Cellular stress and dysfunction triggers prionoid-like phase transition of the NLR pyrin domain containing 3 (NLRP3) inflammasome to assemble supramolecular complexes responsible for mediating immune responses, including the release of inflammatory cytokines—IL-1β and IL-18 [212][213][214][215][216]. The NLRP3 inflammasome is a multiprotein complex comprising the NLRP3 sensor, the apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (ASC) adaptor, and the caspase-1 (CASP1) protease [217][218]. The activation of NLRP3 inflammasomes is inextricably linked to various types of cell death, including pyroptosis, apoptosis, necroptosis, and ferroptosis [217]. Elevated ROS and mitochondrial distress translocate CL from the inner mitochondrial membrane (IMM) to the outer mitochondrial membrane (OMM) [219], and NLRP3 must be primed and directly bound by externalized CL before it can be activated [220]. As discussed in Section 5.1, viroporin ion channel activities activate NLRP3 inflammasome, and COVID-19 severe pathology resulting from an overactive immune-inflammatory response can be exacerbated by the activation of NLRP3 in infected macrophages in humanized mouse model of COVID-19 [221]. The SARS-CoV-2 E protein viroporin increases NLRP3 inflammasome activation in both murine and human macrophages in a biphasic manner [222] by first suppressing NLRP3 inflammasome activation to aid viral replication leading to advanced disease states that promote the activation of NLRP3

inflammasomes [222]. The activation of NLRP3 inflammasome is often associated with the development of severe COVID-19 [223][224][225] and increased oxidative stress [226], while the production of inflammatory cytokines, including IL-β, may fuel the development of cytokine storms and excess oxidative stress to complete a positive feedback cycle [227][228][229][230][231] that enhances N protein LLPS [232]. This unique biphasic effect may be a reflection of how the SARS-CoV-2 virus interacts with DDX3X and stress granules (SGs) during viral replication.

The regulation of the prionoid transition of NLRP3 inflammasome into supramolecular complexes is mediated by DEAD-box helicase 3 (DDX3X or DDX3)—a host X-chromosome encoded DEAD-box RNA helicase that is often hijacked by SARS-CoV-2 and other viruses [233][234]. In total, 18 species of virus from 12 genera—including the dengue virus [235], HIV-1 virus [236][237], hepatitis C virus [238], Japanese Encephalitis virus, and the Zika virus [239]—have been determined to be dependent upon DDX3X for virulence [240]. The ATP-bound form of DDX3X is necessary for the scaffolding of the ASC domain to transition into irreversible, stable, and insoluble supramolecular prionoid-like assemblies [213]. DDX3X is also a critical regulator of SGs requisite for proper SG maturation [241]. Therefore, the formation of SGs and the assembly of NLRP3 inflammasomes become mutually exclusive, since both SGs and NLRP3 inflammasomes compete for the same DDX3X. Consequently, loss of DDX3X will inhibit both SGs maturation and the scaffolding of ASCs to disrupt NLRP3 inflammasome supramolecular assembly [242][243], while the disassembly of SGs may encourage the aggregation of NLRP3 inflammasomes. Lipid peroxidation that can translocate CL from the IMM to OMM is regarded as a hallmark of severe COVID-19 [198]. Monocytes from severe COVID-19 patients exhibit elevated, persistent presence of ROS and lipid peroxidation compared to mild disease and health controls. The level of lipid peroxidation is strongly correlated with CASP1 activity and ASC aggregate formation, responsible for the NLRP3 inflammasome-dependent IL-β secretion by monocytes [244].

Melatonin targets DDX3X to regulate and enhance innate antiviral responses that suppress viral replication. Viral infection induces cellular stress and mitochondrial distress that activates the host integrated stress response (ISR) resulting in the formation of SGs. The timely, adequate presence of melatonin can reduce ROS and lipid peroxidation to prevent the translocation of CL to OMM, thus inhibiting the activation of NLRP3 and its prionoid phase transition to form inflammasome supramolecular complexes [211][245][246][247][248]. This effectively allows DDX3X to accelerate the formation and maturation of SGs that can enhance antiviral innate immune signaling [249] and also inhibit viral protein accumulation and replication [250][251]. As such, viruses including SARS-CoV-2 have evolved sophisticated mechanisms to hijack DDX3X by disrupting SG formation. The SARS-CoV-2 N protein not only phase separates to form “viral factory” condensates [252] that protect the viral genomic RNA by packing them into distinct RNP complexes [253][254], but also acts as the central hub for DDX3X interactions [255]. In Vero E6 cells infected by SARS-CoV-2, mass spectrometry analysis revealed DDX3X localizes with viral RNA foci in cytoplasm, and enhances viral infection via interactions with N protein [256]. The fact that the immunopurified complexes were harvested 24 h post-infection may also imply that the N protein has already undergone phase separation to form viable “viral factories” that can interact with DDX3X, facilitating immune evasion and suppression.

6. DDX3X Is a “Double-Edged Sword” That Mediates Host Antiviral Immunity and Viral Replication

DDX3X is not only an essential mediator of host innate immunity, but also acts as host factors that assist viral replication [257][258]. Therefore, DDX3X is often targeted and hijacked by viruses during infection to evade immune response and promote replication [240][259][260]. SARS-CoV-2 N protein sequesters and potentially binds to DDX3X in order to inhibit host antiviral pathways [255]. The induction of first line IFN immune defense requires the synergistic activation of the type I IFN-β promoter by DDX3X, and TANK-binding kinase 1 (TBK1) and its interaction partner, DDX3X [154][261]. This synergistic effect on IFN induction is mediated by the recruitment of DDX3X into mitochondrial antiviral-signaling protein (MAVS, IPS-1) to promote the scaffolding and aggregation of MAVS into prion-like complexes that can then activate TBK1 and interferon regulatory factor 3 (IRF3) for type I IFN responses [262][263]. LLPS of N protein inhibits both the polyubiquitination and formation of prion-like aggregates in MAVS, effectively suppressing the host innate antiviral response [264]. The prion-like conformational switch of MAVS on the mitochondrial membrane is the lynchpin that propagates antiviral signaling cascades that can inhibit viral infections [265] and is mediated by DDX3X. Nevertheless, in order to hijack DDX3X, viruses including SARS-CoV-2 must first dismantle the assembly of host SGs that are associated with DDX3X.

7. N Protein Must Phase Separation to Target G3BP1 and Disassemble Stress Granules

Stress granules (SGs) are membraneless organelles assembled as a result of LLPS activated by cellular stress, including viral infections [266][267]. Ras-GTPase-activating protein SH3 domain-binding protein 1 (G3BP1) [268] is the molecular switch that regulates RNA-dependent LLPS of SGs, and its effects on SG LLPS can be tuned by phosphorylation of IDRs in G3BP1 as well as extrinsic binding factors that can strengthen or weaken the SG assembly [269]. G3BP1 promotes SG IFN signaling, enhancing innate antiviral response via positive regulation of RIG-1—an upstream target of MAVS [270][271][272]. Recent biochemical and structural analyses of the interactions between SARS-CoV-2 N protein and G3BP1 revealed that N protein residues 1–25 ($N_{1–25}$) occupies a conserved surface groove of the NTF2-like domain of G3BP1 ($G3BP1_{NTF2}$). The interactions between the $N_{1–25}$ and $G3BP1_{NTF2}$ are enhanced by strong surface complementarity and hydrophobic groove-insertion mechanisms, resulting in the inhibition of SG assembly. However, the underlying mechanism for SG disassembly by SARS-CoV-2 N protein could not be determined [273]. N protein binding to G3BP1 also rewires the G3BP1 mRNA binding profile to suppress host cell stress response [274]. In order to target G3BP1, the SARS-CoV-2 N protein must first undergo LLPS, partitioning into SGs before it can bind and interact with G3BP1 to dismantle assembly of SGs [275].

8. The Formation of “Viral Factories” by N Protein LLPS Is Tuned by Phosphorylation

Oxidative stress induces the formation of SGs [276], and N protein LLPS induced by oxidative stress in vitro facilitates its partitioning into SGs to sequester G3BP1 [232][277]. Similar to other condensates formed via LLPS, N protein condensates can be tuned by the concentration of RNA where increasing RNA gradient with a fixed protein concentration at 10 μM caused N protein to increase viscosity from droplets to gel-like, and, eventually, solid assemblies [275][278], whereas phosphorylation of the serine/arginine (S/R)-rich region in the central IDR of the N

protein can tune the viscosity and modulate N protein condensate assembly [279]. Phosphorylation is an ATP-dependent, post-translational modification that can fine-tune molecular interactions of condensate components by inducing nonequilibrium thermodynamic chemical reactions to control the size and number of condensates, acting somewhat like a rheostat that can adjust the dynamics of LLPS during condensate formation [280].

Unphosphorylated N protein facilitates tight association with host mRNAs, and thus, increases the propensity to form gel-like condensates; conversely, phosphorylation of N protein results in the formation of more dynamic, low-viscosity, liquid-like droplets [281]. The EBOV N protein-induced dynamic phosphorylation and dephosphorylation of VP30—the fourth N protein essential for viral transcription—take place in viral inclusion bodies [282][283]. Molecular dynamics simulations revealed that phosphorylation of the phosphate groups at different serine residues in the serine-arginine (SR)-rich domain in SARS-CoV-2 N protein induced the formation of dense salt bridge networks, increasing intra- and intermolecular contacts that impaired contact with RNA derived from SARS-CoV-2 genome, effectively preventing association with nonspecific RNA [253][284]. Thus, the tuning of the physical properties of N protein condensates via phosphorylation can determine whether viral transcription or packaging is favored via hyperphosphorylation (low-viscosity) or hypophosphorylation (high-viscosity), respectively [279][284]. Consequently, high-viscosity, unphosphorylated condensates are more effective at promoting viral packaging—the cytoplasmic compartmentalization of the viral genome—whereas low-viscosity, phosphorylated condensates operate as dynamic “viral factories” to promote viral transcription/replication and host immune evasion [279][281].

9. Melatonin Disrupts Formation of “Viral Factories” by Regulating GSK-3 Phosphorylation of N Protein Condensates

The GSK-3 kinase is implicated in enhancing virus replication, assembly, and release [285][286][287]. As part of the innate antiviral response, GSK-3 acts as a signaling molecule that may be involved in the sensing of nucleic acids of RNA and DNA viruses. It is not only responsible for the rapid activation of type I IFN signaling cascades [288], but also serves as the crux of multiple cell signaling pathways during various stages of viral replication [289]. The activation of GSK-3 in infected cells may be responsible for increased replication and pathophysiology by promoting systemic inflammation, renal dysfunction, and hepatotoxicity via the regulation of cytokine production and cell migration [290][291], as well as the transcriptional regulation of nuclear factor kappa B (NF-κB) [292]. GSK-3 also elevates oxidative stress in infected cells by downregulating the Nrf2 and the Nrf2/antioxidant response element (ARE) pathway [293][294]. GSK-3 directly inhibits nuclear factor erythroid 2-related factor (Nrf2) activation and indirectly inhibits Nrf2 post-induction [295]. The increased oxidative stress from GSK-3 activities may induce the assembly of SGs, but more importantly, the activation of GSK-3 may actually be the elusive, underlying mechanism that is responsible for the disassembly of SGs by SARS-CoV-2 N proteins [273]. The phosphorylation of N protein by GSK-3 not only determines the viscosity and function of condensates formed by N protein LLPS, but GSK-3 can also regulate DDX3X functions to control stress granule assembly and disassembly (**Figure 1**). GSK-3 is responsible for the phosphorylation of Gle1A which is is recruited to SGs in the cytoplasm during stress to regulate SG dynamics, assembly, and disassembly by controlling how DDX3X binds to RNA [296][297]. Phosphorylation of

Gle1A by GSK-3 alters the biochemical properties and electrophoretic mobility that allows Gle1A to bind and inhibit DDX3X ATPase activities that ultimately results in the disassembly of SGs.

Melatonin suppresses hyperphosphorylation of N protein by inhibiting the gene expression of GSK-3 and deactivating GSK-3 by promoting its phosphorylation. In Neuro2A cells subjected to okadaic acid (OA) treatment to induce phosphorylation of tau by GSK-3β exhibited elevated ROS and cytotoxicity, resulting in the loss of cell viability of up to 60%. Incubation with 200 μM melatonin for 24 h completely reversed tau-induced cytotoxicity, while at 100 μM concentration, melatonin completely restored cell viability, where melatonin effectively reduced the total mRNA expression level of GSK-3β [298].

Additionally, in human mesenchymal stem cells, melatonin attenuated adipogenic differentiation by suppressing GSK-3β activities [299]. Male Wistar rats subjected to bilateral renal ischemia to induce ischemia/reperfusion (I/R) injury showed increased lipid peroxidation and elevated lactate dehydrogenase (LDH) in plasma compared to controls. Treatment with melatonin (10 mg/kg, i.p.) 30 min before renal clamping markedly reduced lipid peroxidation and LDH levels in plasma, while the phosphorylation of GSK-3β was significantly enhanced via the restoration of AKT phosphorylation in the melatonin-treated group [300].

10. Conclusion

As COVID-19 transitions inevitably from pandemic to endemic, it is presently unclear how continued endemic infections from evolving SARS-CoV-2 variants will shape human health in the years to come. The detrimental effects of viral replication and persistence causing excess oxidative stress and mitochondrial distress can result in downstream effects that alter both host and viral RNA methylomes. Consequently, SARS-CoV-2 introduces a complex, fertile landscape that fosters a wide-array of challenging and often unexplained manifestations [301] during acute infection and post-infection. The timely application of melatonin as an essential adjuvant during acute infection and recovery can inhibit viral infection, replication, and persistence to prevent the hijacking of mitochondria and other vital host resources associated with immune evasion and suppression.

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Abbreviations

Ca^{2+}	calcium
CL	cardiolipin
DNA	deoxyribonucleic acid
EBOV	Ebola virus
GSK	glycogen synthase kinase
IBM	inner boundary membrane

IDR	intrinsically disordered region
IFN	interferon
IMM	inner mitochondrial membrane
I.P.	intraperitoneal
ISG	interferon-stimulated gene
ISR	integrated stress response
JAK-STAT	Janus kinase-signal transducers and activators of transcription
K^+	potassium ion
LINE1, L1	long interspersed nuclear element 1
m^6A	N^6-methyladenosine
METTL3	methyltransferase 3
METTL14	methyltransferase 14
mPTP	mitochondrial permeability transition pore
mRNA	messenger RNA
NLRP3	NLR pyrin domain containing 3
Nrf2	nuclear factor erythroid 2-related factor
PBMC	peripheral blood mononuclear cells
PI	post-infection
RBP	RNA-binding protein
RIRR	ROS-induced ROS release
RNA	ribonucleic acid
RNA-seq	RNA sequencing
RNP	ribonucleoprotein
ROS	reactive oxygen species
RT	reverse transcriptase
RTE	retrotransposable element, retrotransposon

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SG	stress granule
S/R	serine/arginine
TE	transposable element
VSV	vesicular stomatitis virus
YTHDF2	YTH-domain family 2
ZIKV	Zika virus

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