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Glycogen synthase kinase-3: A putative target to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic

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ABSTRACT

The coronavirus disease 19 (COVID-19) outbreak caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) had turned out to be highly pathogenic and transmittable. Researchers throughout the globe are still struggling to understand this strain’s aggressiveness in search of putative therapies for its control. Crosstalk between oxidative stress and systemic inflammation seems to support the progression of the infection. Glycogen synthase kinase-3 (Gsk-3) is a conserved serine/threonine kinase that mainly participates in cell proliferation, development, stress, and inflammation in humans. Nucleocapsid protein of SARS-CoV-2 is an important structural protein responsible for viral replication and interferes with the host defence mechanism by the help of Gsk-3 protein. The viral infected cells show activated Gsk-3 protein that degrades the Nuclear factor erythroid 2-related factor (Nrf2) protein, resulting in excessive oxidative stress. Activated Gsk-3 also modulates CREB-DNA activity, phosphorylates NF-κB, and degrades β-catenin, thus provokes systemic inflammation. Interaction between these two pathophysiological events, oxidative stress, and inflammation enhance mucous secretion, coagulation cascade, and hypoxia, which ultimately leads to multiple organs failure, resulting in the death of the infected patient. The present review aims to highlight the pathogenic role of Gsk-3 in viral replication, initiation of oxidative stress, and inflammation during SARS-CoV-2 infection. The review also summarizes the potential Gsk-3 pathway modulators as putative therapeutic interventions in combating the COVID-19 pandemic.

1. Introduction

In late December 2019, Wuhan, China, got attention worldwide after getting several patients diagnosed with pneumonia, following a viral infection. On 11th February 2020, the pathogenic strain of the virus was taxonomically designated as “Severe Respiratory Syndrome Coronavirus...
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The severity of symptoms and death in SARS-CoV-2 infected patients depends on the viral infection and is greatly affected by the aggressive behaviour of the host immune system. COVID-19 patients’ systemic cytokine profile shows a close resemblance with cytokine release syndrome, characterized by macrophage activation, an elevated level of cytokines like tumour necrosis factor-alpha (TNFα), interleukin-6 (IL-6) and interferon-gamma (IFN-γ) [16]. Further, elevated levels of these cytokines trigger ARDS, characterized by a low level of oxygen in blood and difficulty in breathing, leading to the death of the infected patients [17].

Severe hospitalized COVID-19 patients’ blood plasma exhibits a higher level of granulocyte colony-stimulating factor (G-CSF), IL-2, IL-6, IL-10, monocyte chemoattractant peptide (MCP-1), macrophage inflammatory protein 1α (MIP1α) and TNFα [32]. The blood plasma of the infected patients shows a significantly higher level of IL-6 in severe cases compared to mild or non-severe cases, which further contributes to...
macrophage activation syndrome [31]. Pulmonary infiltration-based assessment in ARDS patients also revealed that a more significant portion of lung injury is associated with a higher level of IL-6 in peripheral blood [33]. All of these evidences suggest that SARS-CoV-2 infection is responsible for dysregulation of the host immune system with the abnormal synthesis of cytokines, chemokines, and a decrease in the level of lymphocytes that ultimately leads to cytokine storm responsible for multi-organ failure.

3.1. Role of Nuclear factor-κB in disease progression

Nuclear factor-κB (NF-κB) is the leading player that responds immediately following the pathogen’s invasion by promoting inflammation, controlling cell proliferation, and survival. NF-κB is a heterodimeric transcription factor that belongs to the Rel protein family. There are 05Rel proteins present in mammalian cells that further divided into two classes. RelA (p65), RelB, and c-Rel are grouped in first-class, while NF-κB1 (p50) and NF-κB2 (p52) belongs to the second group that is devoid of transcriptional-modulation activity. So, both the classes of characterized by the presence of transactivation domain, while NF-κB proteins present in usual cell signalling cascades. ROS are oxygen molecules with

SARS-CoV-2 infection and further progression of pathogenic conditions [35,36]. NF-κB is a transcription factor that controls the expression of proinflammatory genes responsible for the cytokine storm. A study suggested that the nucleocapsid protein of SARS-CoV directly interacts with NF-κB, translocate it to the nucleus, and finally upregulates IL-6 gene expression [37]. Several studies indicated that SARS-CoV directly or indirectly activates NF-κB protein, following infection [38-40]. NF-κB also activated by receptors present on the cell surface membrane-like, Toll-like receptor 4 (TLR 4). Pathogen associated molecular pattern (PAMP) and Death associated molecular pattern (DAMP) are inflammatory, stimulating molecules released by virus-infected cells, which act as ligands for TLR 4, subsequently activating NF-κB protein via MyD88-dependent pathway [7]. Oxidative stress is another important factor responsible for cytokine storm generation via cross-talk between Nuclear factor erythroid 2-related factor (Nrf2) and NF-κB pathway. NF-κB suggested as a negative regulator of Nrf2 driven genes, either by recruiting histone deacetylase 3 (HDAC3), which promote local histone hypoacetylation or deprive the CBP (CREB binding protein) [7, 41].

4. SARS-CoV-2 infection and oxidative stress

Oxygen is a crucial molecule in the aerobic system to maintain normal life processes. Under normal cellular conditions, the oxygen molecule utilized to generate chemical energy in the form of ATP in a very tight and controlled manner. The oxygen molecule combustion generates a small number of reactive oxygen species (ROS), which utilized for usual cell signalling cascades. ROS are oxygen molecules with
an unpaired electron that behaves as free radicals and reactive metabolites. Several ROS forms were discovered so far, such as peroxidase, oxygen-free radicals, nitrogen oxide, and singlet oxygen molecules \[7\]. Generally, ROS associated cellular damage is processed via sophisticated antioxidant machinery, involving both enzymatic (Catalase (CATs), Superoxide dismutase (SODs), and glutathione peroxidase (GPx) and non-enzymatic (Glutathione and nicotinamide adenine dinucleotide phosphate hydrogen [NAD(P)H] mechanisms \[7\]. In normal physiological conditions, the antioxidant systems can work simultaneously to combat the exceeded levels of ROS. However, in a pathological state, ROS overwhelmed the antioxidant mechanism and generated “oxidative stress” in cells. All the crucial cellular components such as proteins, lipids, nuclear, and mitochondrial DNA get degraded under the influence of oxidative stress, subsequently triggering the process of cell death.

The available literature of clinical and preclinical experiments proposed that oxidative burst is another prompting factor for mortality following SARS-CoV infection \[42,43\]. SARS-CoV-2 infection activates the host airway epithelium and alveolar macrophage, further releasing cytokines to attract another immune cell from the blood (Neutrophils and monocyte that further differentiate into macrophage) at the site of injury. Recruitment of these cells ensures the clearance of the virus, but due to imbalanced host immune system, they also start to release excessive cytokines that further aggravate to cytokine storm. The recruited phagocytic cell participates in ROS generation, along with inflammatory response \[43\]. Nicotinamide adenine dinucleotide phosphate oxidases (NADPH oxidase) and xanthine oxidase (XO) are the two well-known enzymes responsible for oxidative stress in respiratory viral infections \[44\]. NADPH oxidase (NOX) is an evolutionary conserved, membrane-bounded enzyme complex that catalyzes the molecular oxygen into superoxide \[44\]. Human’s NADPH oxidase family consists of 7 members, NOX1–5, DUOX1, and DUOX2 \[45\]. Its C-terminal region comprises NADPH binding site, flavin adenine dinucleotide binding domain, while the N-terminal region consists of 6 transmembrane α helical domains, with four conserved heme-binding sites \[45\]. NOX2 is predominantly expressed in the recruited phagocytes (neutrophils and macrophages) at the viral infection site and contributes to oxidative stress \[46\]. A study reported that alveolar macrophage depended oxidative stress is responsible for acute lung injury progression following H5N1 viral infection in mice, mostly via oxidized phospholipid and superoxide. However, the same pathological events reduced following the suppression of p47phox, a regulatory subunit of NOX2 \[19\]. In a study, Influenza A virus-infected NOX2-/y mice showed reduced oxidative stress, improved alveoli epithelium condition, less production of superoxide, and reduced airway inflammation compared to wild type mice (Fig. 2) \[46\].

Similarly, ex-vivo influenza A virus-infected alveolar macrophage exhibited an increase in superoxide synthesis via NOX2 enzyme complex \[47\]. Xanthine oxidase (XO) is another ROS generating enzyme that participates in oxidative stress, following respiratory viral infection. In the mammalian system, this enzyme is existing in interchangeable form between XO to Xanthine oxidoreductase (XOR) \[7\]. XOR is predominantly distributed in healthy tissues and reduces NAD\(^+\) to NADH by utilizing electron form substrate. While during inflammation, XOR is converted into XO by oxidation of cysteine amino acid or calcium-dependent proteolysis. XO shows more affinity toward

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**Fig. 2.** Possible mechanism of oxidative stress in COVID-19 patients following SARS-CoV-2 infection.

Proinflammatory cytokines and chemokines are released by the SARS-CoV-2 infected cells, to attract the phagocytes. Airway epithelium and phagocytic cells (Neutrophils and Monocyte derive macrophage) carry different isoforms of NOXs, which trigger the generation of superoxide ions during cellular stress condition and directly participate in oxidative stress. Xanthine oxidoreductase is also transformed into xanthine oxidase -during stressed cellular environments and triggers ROS generation by metabolizing hypoxanthine. Tumour necrosis factor (TNF) also enhances oxidative stress by initiating the NF-κB pathway and inhibiting the complex II of the electron transport chain.

**TNF:** Tumor necrosis factor; **TNF-R:** Tumor necrosis factor receptor; **ATP:** Adenosine triphosphate; **XOR:** Xanthine oxidoreductase; **XO:** Xanthine oxidase; **ARE:** Antioxidant Response Element; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **O\(_2^−\):** Oxygen molecule; **O\(_2^*\):** Superoxide anion.
molecular oxygen, resulting in the transfer of a univalent and divalent electron to oxygen that further generates superoxide and hydrogen peroxide, respectively (Fig. 2) [48]. In-vitro rhinovirus’s infection in primary bronchial and A549 respiratory epithelial cell lines decreased the intracellular glutathione (GSH) level, leading to oxidative stress via enhanced superoxide production. Serine protease inhibitor or XO inhibitor, oxypurinol treatment enhanced the intracellular levels of GSH, and decreased superoxide generation, thus revealed that XO also participates in oxidative stress during infection [49]. In-vivo analysis also revealed that XO is the main contributor to superoxide synthesis during a respiratory viral infection. Mice infected with influenza virus showed a higher mortality rate, which found to be associated with XO and superoxide in BALF and serum analysis. However, allopurinol and chemical modified superoxide dismutase decreased the oxidative stress and mortality rate [50]. These evidences revealed that XO also participates in the viral associated disease progression via oxidative stress. A part of these activated phagocyte releases pro-oxidant mediators such as TNF and IL-1, which further enhances the oxidative stress in host cells during viral infection. TNF binds with the complex II of the mitochondrial respiratory chain, hampering oxidative phosphorylation via restricting electrons transport. As a result, the electron transport chain becomes leaky, and lastly, it enhances superoxide production [51]. TNF also helps in detachment of NF-xB protein from IKB complex, resulting in suppression of antioxidant gene expression via binding to their promoter region following translocation from the cytoplasm to the nucleus [52] (Fig. 2). During stress condition, neutrophils also release lactoferrin along with lysosomal proteins under the influence of IL-1, which further binds to iron and start to accumulate in the reticuloendothelial system. When an iron-binding threshold reached, superoxide ions combine with free iron to generate hydroxyl radicals via Fenton reaction and enhances oxidative stress [53,54].

4.1. Nrf2 a key regulator of antioxidant genes

Nrf2 is the main transcription factor that plays an important role to overcome oxidative stress. It is a basic leucine zipper (bZIP) protein that belongs to the cap 'n' collar family of transcription factors. Nrf2 consist of 6 highly conserved functional domains termed as Neh 1–6 (Nrf2-ECH homologies 1–6). Neh1 is a leucine zipper domain through which Nrf2 interact with other transcription factors, whereas Neh2 is the Kelch-like ECH associated protein 1 (Keap1) binding domain [55]. Keap1 is a cystine rich and cytoplasmic protein, whose N-terminal domain binds with Cul3-dependent E3 ubiquitin ligase complex, while C-terminal domain binds with Nrf2 protein. Under normal physiological conditions, Keap1 protein ubiquititates the Nrf2 resulting in its proteasomal degradation [55].

However, during stress conditions Nrf2 detached from the Keap1 protein, translocate to the nucleus, heterodimerize with small muco-loapneurotic fibrosarcoma (MAFs) proteins, and finally initiates or suppresses the transcription of genes that consists of electrophile response elements (ERE) or antioxidant response elements (ARE) in their promoters [7]. Nrf2 regulates more than 500 genes expression belonging to oxidative stress, inflammation, autophagy, metabolism and excretion [55]. The pulmonary system is more exposed to oxidative stress because of its highly vascular nature and indirect contact with environmental oxidant, which had already proven in numerous respiratory diseases. It was found that, lung-specific Nrf2 conditional knockout rodents showed pulmonary protective behaviour in respiratory disorders [56].

5. Systemic oxidative stress and inflammation linked thrombus formation in SARS-CoV-2 infection

Abnormal coagulation, a higher level of D-dimers, and low platelet count are the signs of poor prognosis and significant reasons for multiple organ failure and death in severe cases of COVID-19 [57,58]. Microthrombus had reported in the lungs, the heart, the kidneys, and the brain of COVID-19 patients [59,60]. Cytokine storm induces aberrant coagulation by expressing the tissue factor (TF) pathway [61,62]. TF is a member of cytokine receptor superfamily and type I integral membrane glycoprotein, which is highly abundant in the vasculature sub-endothelium, especially in the brain, lungs, gut, skin, as well as in the monocytes. In response to proinflammatory cytokines, especially IL-6, the expression of TF is upregulated in the monocytes and the perivasculars cells, resulting in TF exposure to circulation [63,64]. The exposed portion of TF forms a complex with circulating factor VII, thus enhance its catalytic activity that further activates downstream circulating factors, such as IX and X. Activated factor X participates in the transformation of prothrombin into thrombin, that finally leads to the formation of blood clots by conversion of fibrinogen into fibrin [65,66] (Fig. 3).

Platelet activation, different proinflammatory events, and fibrin clot formation are the main consequences of the cytokine storm that also provokes thrombin production via protease-activated receptors (PAR) signalling pathway. PAR is a unique G-protein coupled cell surface receptor that carries its ligand and remains inactive until unmasked by proteolytic cleavage by the TF-factor-VIIa complex [67]. Thrombin mediated PAR activated platelets undergo a morphological transformation, release platelet activators such as serotonin, adenosine diphosphate (ADP), thromboxane A2, translocate cell adhesion molecule P-selectin and CD40 ligand on the surface of platelet along with activation of the integrin albb/h3 receptor [67]. The released thromboxane A2 and ADP trigger activation of neighbouring platelets via thromboxane receptor and P2Y12, respectively [68]. Activated albb/h3 on platelets’ surface binds with von Willebrand factor (vWF) and fibrinogen that contributes to platelet aggregation [67]. Activated endothelial cells following PAR signalling also exposes cell adhesion molecules (E-selectin, P-selectin, ICAM-1 and VCAM-1) and expresses monocyte chemotaxtactant protein-1, that facilitates recruitment, adhesion, and migration of leukocytes and platelets during viral infection [69]. Adherent leukocyte-platelets interaction provides positive feedback to amplify the overall inflammatory response and pro-coagulation events [69]. These events are prothrombotic, which further contributes to blood clot formation (Fig. 3).

Along with cytokine storm, oxidized phospholipids (OxPLs) also participate in the coagulation cascade via the TLR-4 receptors present on the monocytes and endothelial cells. OxPLs concerned as PAMPs patterns that are recognized by numerous conserved pattern-recognition receptors. In an experimental model of acute lung injury, OxPLs triggered cytokine storm release via TLR4-TRIF-TRAF6-NF-xB pathway. IL-6 further promoted TF expression on monocytes and activated the endothelial cell to express monocyte adherent protein for their requirement, which finally participated in inflammatory events [19]. Thrombotic complications can be reduced in pre-existing metabolic and cardiovascular disorders in COVID-19 patients by interfering with the OxPLs activated monocyte or endothelial cell [36]. Additionally, during inflammation, the natural anticoagulant pathways such as TF pathway inhibitors or antithrombin are nearly diminished, subsequently facilitating coagulation cascade [69].

6. Gsk-3 and SARS-CoV-2 infection

The virus has to undergo many complex processes that are tightly regulated to infect a host cell. It begins with viral genomic RNA entry into the host cytosol, transcription, and finally budding off as viral progeny. These viral progenies are similar to their parent in morphology and function that consists of 4 structural proteins, spike (S) protein, envelope (E) protein, matrix (M) protein and nucleocapsid (N) protein [70]. The N protein of severe acute respiratory syndrome coronavirus is the most abundant protein existing in an infected host cell among all other proteins.

Protein sequencing also revealed that N protein is highly conserved
among the species, which consists of 3 domains, including the N-terminal domain (NTD/domain 1), C-terminal domain (CTD/domain 3) and linker region (LKR/domain 2). N-terminal domain enriched with positive charge amino acids, which is responsible for binding with viral RNA. Whereas, C-terminal domain mapped between 373 and 390 amino acids is enriched with lysine, thought to be responsible for nuclear localization signal [71]. The C-terminal domain of the N protein is also responsible for protein dimerization. Both the domains of N protein i.e., domain 1 and domain 3 are linked to each other through linker region (domain 2) that consists of serine-arginine motif, responsible for the multimerization of the N-protein [72] and predicted as a hot spot region for phosphorylation. In brief, N-protein divided into three main domains that play diverse functions during different stages of the virus life cycle. N-protein is a type of capsid protein whose primary function is to pack the virus’s genomic RNA into the protective covering.

Interestingly, to perform such activity, N-protein should recognize the viral genomic RNA, associate with it, and finally, oligomerize by self-association to form capsid or nucleocapsid. Protection of viral genome, timely replication, and proper transmission is the capsid or nucleocapsid [71]. N-protein also inhibits host cell proliferation and cytopathic effects following the treatment of Gsk-3 inhibitor kenpaullone and lithium chloride, thus suggested phosphorylation by this kinase be strongly linked with the viral replication [74]. Several sub-genomic mRNAs synthesized due to discontinuous transcription mechanisms during the coronavirus replication, which encodes major structural proteins [75]. Translation regulating sequence (TRS) responsible for the discontinuous transcription process exists in front of each gene (body TRS) and after the leader sequence (leader TRS) [76]. Template-switching events happen via base pairing between the body TRS and leader TRS to synthesize the discontinuous minus-stranded RNAs. Discontinuous nested plus-strand sub-genomic mRNA transcribed from the previously generated minus-stranded RNAs [77]. This discontinuous transcription mechanism tightly controlled for the successful compilation of the virus life cycle. Among all the structural proteins, N-protein tightly regulates the discontinuous transcription mechanism as the synthesis of sub-genomic mRNA is reduced following the N segment’s deletion from the replicon [78]. The studies showed that phosphorylated N-protein at serine-arginine motif also inhibits the translational machinery of the virus [72] and interferes with antiviral response signalling. All this evidence suggested that Gsk-3 protein plays a crucial role in the virus life cycle and disrupts host-defence mechanisms for the infection progression.

As described, ROS’s overproduction and alteration in antioxidant mechanisms are mainly responsible factors for the viral replication and development of associated conditions [6]. Nrf2 is a transcription factor responsible for combating the oxidative stress by upregulating antioxidant genes that consist of ARE in their promoter [7]. The respiratory syncytial virus-infected Nrf2 knockout mice showed severe infection and increased viral titer, enhanced mucous secretion, inflammation, and epithelium injury compared to the wild type mice [80]. Besides, influenza-infected Nrf2 knockout mice, following cigarette smoking, could not combat oxidative stress and showed higher mortality...
compared to wild-type strain due to higher secretion of mucous and peri bronchial inflammation [80]. Similarly, the direct correlation of oxidative stress markers with SARS-CoV infection is remarkably observed in various animal model systems [80]. Gsk-3β, a direct up-stream regulator of Nrf2 found to be active in numerous virus-infected cells. It also participates in disease progression by supporting the replication process or inhibiting the host defence mechanisms [81]. Active Gsk-3β phosphorylates Nrf2 on serine reside of Neh6 domain that finally gets degraded by cullin-1/Rbx1-mediated ubiquitination process, and provokes oxidative stress [7]. HO-1 expression was also significantly upregulated following Gsk-3β inhibition in Huh 7.5.1 hepatocytes infected with JFH1 hepatitis C virus (HCV) [82]. These literature findings strongly support the role of Gsk-3 in oxidative stress following viral infection (Fig. 4).

Gsk-3 involvement is not only restricted up to oxidative stress, but it also provokes systemic inflammation for disease progression by synthesizing the pro-inflammatory molecules such as IL-6, IL-1β, IL-18, IFN-γ and TNF-α [81]. Gsk-3β mainly participates in inflammatory reactions via TLRs [83]. TLRs are a type of pattern recognition receptors that responds to PAMs released by the virus-infected cell. Coronavirus-virus-infected organism shows a significant upregulation of OxPLs, which act as PAMs. OxPLs induces the production of pro-inflammatory cytokines by translocation of NF-κB from the cytosol to the nucleus via TLR4–TRIF–TRAF6 pathway [6]. β-catenin protein, a direct downstream target of Gsk-3β, forms a complex with both the units of NF-κB, alters its DNA binding activity that ultimately inhibits inflammatory cascade. Activated Gsk-3β phosphorylates β-catenin protein for proteasomal degradation that directly promotes the inflammatory events [84]. In a study, it was found that Gsk-3β directly phosphorylated P65 unit of NF-κB at ser276, enhanced CBP-P65 interaction, followed by...

Fig. 4. Putative role of Gsk-3 in the SARS-CoV-2 replication and COVID-19 pathogenesis. Activated Gsk-3 phosphorylate the nucleocapsid protein of SARS-CoV-2 and support viral genome replication and transcription. Simultaneously, activated Gsk-3 also phosphorylate and degrade the significant oxidative stress combating transcription factor Nrf2, resulting outburst of different reactive oxygen species. Circulating DAMPs and PAMPs bind with TLR4 and stimulate the pro-inflammatory cytokine synthesis via Myd88 dependent pathway. β-catenin is a downstream protein of Gsk-3, phosphorylate the p50 sub-unit of Nrf2, altered their DNA binding ability, and suppresses inflammatory events. CREB is another transcription factor that initiates the expression of anti-inflammatory genes to overcome the disease condition. During virus infection, activate Gsk-3 degrade the β-catenin protein and phosphorylate the CREB, consequential, lost CBP binding site, and enhances pro-inflammatory cytokine synthesis, especially IL-6. LiCl and Tidelglusib are the two well-known non-selective metal cation and non-ATP competitive inhibitors of Gsk-3.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; N-protein: Nucleocapsid protein; sgRNA: Subgenomic messenger RNA; DAMPs: Death-associated molecular pattern; oxPIs: Oxidized phospholipids; TLR: Toll like receptor; Gsk-3: Glycogen synthase kinase; Keap1: Kelch-like ECH-associated protein 1; Nrf2: nuclear factor erythroid 2-related factor 2; Cul3: Culin 3; CREB: cAMP response element-binding protein; CBP: CREB binding proteins; ARE: Antioxidant Response Element References; Myd88: Myeloid differentiation factor 88; IRAKs: Interleukin (IL)-1R-associated kinase; TRAF6: Tumour necrosis factor receptor associated factor 6; TAK1: Transforming growth factor-β (TGF-β)-activated kinase 1; IkB: Inhibitor of kappa B; TIRAP: TIR-domain-containing adaptor protein; LiCl: Lithium chloride.
transcription of pro-inflammatory gene expression [85]. Activated Gsk-3β also reduced CREB-DNA interaction via phosphorylation at Ser15 and reduced IL-10 [7] (Fig. 4).

7. Gsk-3 pathway modulators and SARS-CoV-2 infection

Gsk-3 shows a remarkable impact on numerous physiological processes and plays a crucial role in the pathogenesis of various clinical conditions. Lithium is a non-selective metal cation most frequently used as a Gsk-3 inhibitor to treat patients diagnosed with mood and bipolar disorders [8,91]. A study found that lithium chloride (LiCl) treatment helped overcome the transmissible gastroenteritis coronavirus infection in porcine [86]. Similarly, replication and entry of porcine epidemic diarrhea virus (PEDV) in the Vero cells also reduce following E1L-10α [81]. A study found that lithium chloride (LiCl) treatment, involving regulation of SARS-CoV-2 genome transcription and translation, could prove to be the potential success of GSK-3 inhibition in reference to the LiCl treatment [87]. LiCl treatment also protects from the coronavirus infection in porcine [86]. Similarly, replication and entry of porcine epidemic diarrhea virus (PEDV) in the Vero cells also reduce following E1L-10α [81]. A study found that lithium chloride (LiCl) treatment, involving regulation of SARS-CoV-2 genome transcription and translation, could prove to be the potential success of GSK-3 inhibition in reference to the LiCl treatment [87]. LiCl treatment also protects from the coronavirus infection in porcine [86]. Similarly, replication and entry of porcine epidemic diarrhea virus (PEDV) in the Vero cells also reduce following E1L-10α [81]. A study found that lithium chloride (LiCl) treatment, involving regulation of SARS-CoV-2 genome transcription and translation, could prove to be the potential success of GSK-3 inhibition in reference to the LiCl treatment [87]. LiCl treatment also protects from the coronavirus infection in porcine [86]

Moreover, thiadiazolidinone treatment in the double transgenic mouse model of AD showed improved memory formation via enhancing the cascade of proliferation in the stem cell pool, differentiation, migration, and maturation both in in-vitro and in-vivo studies [90].

Moreover, thiadiazolidinone treatment in the double transgenic mouse model of AD showed improved memory formation via enhancing the cascade of proliferation in the stem cell pool, differentiation, migration, and maturation both in in-vitro and in-vivo studies [90]. Further, the virus has a very high mutation rate, while vaccines are apprehended as a striking target. In the process of curbing the pandemic, Gsk-3 can act as a potent therapeutic attribute. Thus necessary efforts must be taken to devise comprehensive and in-depth research towards this target.

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