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Review

Can a metabolism-targeted therapeutic intervention successfully subjugate SARS-COV-2? A scientific rational

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ABSTRACT

As a process entailing a high turnover of the host cell molecules, viral replication is required for a successful viral infection and requests virus capacity to acquire the macromolecules required for its propagation. To this end, viruses have adopted several strategies to harness cellular metabolism in accordance with their specific demands. Most viruses upregulate specific cellular anabolic pathways and are largely dependent on such alterations. RNA viruses, for example, upregulate both glycolysisand glycogenolysis providing TCA cycle intermediates essential for anabolic lipogenesis. Also, these infections usually induce the PPP, leading to increased nucleotide levels supporting viral replication. SARS-CoV-2 (the cause of COVID-19)that has so far spread from China throughout the world is also an RNA virus. Owing to the more metabolic plasticity of uninfected cells, a promising approach for specific antiviral therapy, which has drawn a lot of attention in the recent years,

would be the targeting of metabolic changes induced by viruses. In the current review, we first summarize some of virus-induced metabolic adaptations and then based on these information as well as SARS-CoV-2 pathogenesis, propose a potential therapeutic modality for this calamitous world-spreading virus with the hope of employing this strategy for near-future clinical application.

1. Introduction

A Severe respiratory illness was lately reported in Wuhan, Hubei province, China. Metagenomic RNA sequencing of bronchoalveolar lavage fluids identified a novel virus strain belonging to the family Coronaviridae, named as SARS-CoV-2, and the resultant disease was termed Coronavirus Disease 2019 (COVID-19). By conducting phylogenetic analysis on the complete viral genome, the virus strain was shown to be most closely (75–80 % nucleotide similarity) related to a group of severe acute respiratory syndrome (SARS)-like coronaviruses (subgenus Sarbecovirus, genus Betacoronavirus) previously found in bats in China [1,2].

According to the COVID-19 Situation Report-209 published by the World Health Organization (WHO), a total of 8 21,294,845 confirmed cases and 761,779 deaths have been identified globally until 16 August 2020 [3]. However, there is still no antiviral drug proven effective for definitive treatment of COVID-19, underpining the need for further studies to find an effective and safe treatment for the disease.

Eukaryotic viruses have been shown to induce large-scale changes in host cellular metabolism. Most viruses evaluated to date trigger aerobic glycolysis, which is also known as the Warburg effect. Numerous tested viruses also induce glutaminolysis and fatty acid (FA) synthesis. These alterations of carbon source usage by infected cells can provide specific cellular substrates for viral particles, enhance available energy for viral replication and virion production, thereby creating viral replication niche, while augmenting infected cell survival [4].

A better appreciation of the metabolic alterations required for each virus replication may provide the basis for developing novel therapeutic strategies aimed at targeted inhibition of specific metabolic pathways.

RNA virus (RV) infection induces anabolic reprogramming of the host cell metabolism by 1) Inducing PI3K-mediated trafficking of glucose transporter 1 (GLUT1)-containing vesicles to the host cell membrane, thereby increasing glucose uptake. Also, overexpression of GLUT1 has been found to give rise to increased PPP intermediates 2)

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Upregulating both glycolysis and glycogenolysis which provide TCA cycle intermediates required for anabolic lipogenesis. 3) Activating the PPP that results in enhanced levels of nucleotides supporting viral replication [5].

Since SARS-CoV-2 is also an RV [6], it is therefore expected to induce the same metabolic reprogramming as other RVs for replication in the host cell. Thus, targeting these metabolic pathways could be applied to treat this infection. There is evidence reflecting upregulated glycolysis, PPP and TCA cycle following coronavirus infection [7–16]. Therefore, in the current review, we first summarize some of the virus-induced metabolic adaptations and then, based on this information as well as SARS-CoV-2 pathogenesis, propose a potential therapeutic modality for this calamitous world-spreading virus with the hope of employing this strategy for near-future clinical application.

2. Viruses harness host cell metabolism

A plethora of strategies have been adopted by viruses to ensure the undistributed supply of macromolecules and suit the host cell metabolism according to their specific demands. The high turnover of biomolecules linked with virion production as well as simultaneous activation of cellular defense mechanisms brings about a highly anabolic state that is often associated with upregulated uptake of extracellular carbon sources (like glucose and glutamine) as well as their redirection to metabolic pathways vital for viral replication including lipogenesis and nucleotide synthesis [5].

It has been demonstrated that viruses employ strategies as diverse as the activation of cytosolic signaling, including PI3K [17] and CaMK-K1/AMPK [18,19] or transcriptional regulation like activation of Myc [20,21], SREBP [16,22–25] and ChREBP [26]. The current data point to a dichotomy between RNA and DNA viruses when delving into their respective strategies of host cell manipulation. That is to say, while DNA viruses have been found to control key metabolic pathways at the transcription level [20,21,26], RNA viruses seem to shape host-cell metabolism through post-transcriptional modifications [17], that are in concordance with the pace of the respective replication cycles (Fig. 1).

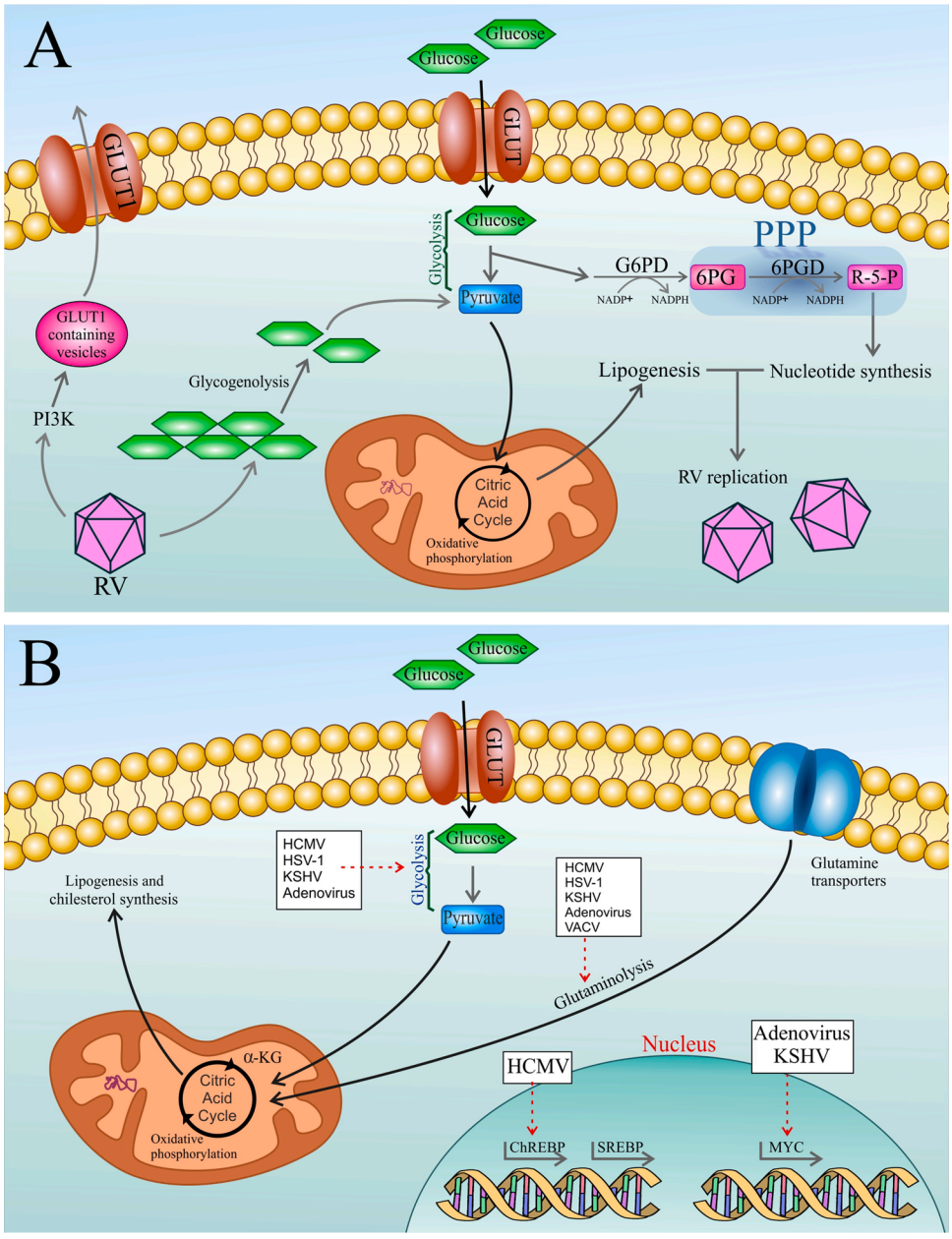

Fig. 1. a) Rhinovirus, as an RNA virus (RV), post-transcriptionally modulates the host cell metabolism. Infection with this virus induces anabolic reprogramming of the host cell metabolism by 1) Inducing PI3K-mediated trafficking of GLUT1-containing vesicles to the host cell membrane thereby increasing glucose uptake. Also, overexpression of GLUT1 has been found to result in increased PPP intermediates 2) Upregulating both glycolysis and glycogenolysis which provides TCA cycle intermediates required for anabolic lipogenesis 3) Activating the PPP which results in enhanced levels of nucleotide that support viral replication. RV: rhinovirus; PI3K: phosphatidylinositol 3-kinase; GLUT: glucose transporter; TCA: tricarboxylic acid cycle. b) Schematic overview representing metabolic targets of some DNA viruses. Various DNA viruses activate particular anabolic metabolic programs following infecting the host cells, to finally support viral replication and virion maturation. Dashed arrows show a virus induced activation of the respective metabolic pathway or a transcription factor activation. TCA: tricarboxylic acid cycle; α-KG: α-ketoglutarate; SREBP: sterol regulatory element-binding protein; ChREBP: carbohydrate-response element-binding protein; GLUT: glucose transporter; HCMV: human cytomegalovirus; HSV-1: herpes simplex virus-1; KSHV: Kaposi's sarcoma-associated herpesvirus; VACV: vaccinia virus.

Host cell FA synthesis machinery has proven substantial for viral genome replication, virion production, and morphogenesis. Numerous viruses instigate the formation of phosphatidylinositol 4-phosphate/cholesterol-enriched membranes to create viral replication complexes (VRCs) at the interface of the host endoplasmic reticulum (ER). Generation of secluded membranes that protect viral nucleic acids from immune surveillance (for example, cytosolic pattern recognition receptors) and encompass an optimal environment for viral replication, requires the accumulation of sterols at the VRCs of RNA viruses [27,28]. VRC formation critically relies on the host cell's sterol synthesis reprogramming by recruiting the phosphatidylinositol-4 kinase III beta and oxysterol-binding protein (PI4KB–OSBP) axis. Thus, perturbation of cellular cholesterol homeostasis dampens viral replication [29–33].

This information highlights the pivotal role of lipogenesis for sustained viral propagation and that targeting of lipogenesis could pave the way for effective inhibition of viral replication.

There is evidence reflecting upregulated glycolysis, PPP, and TCA cycle following coronavirus infection, including:

HCoV-229E could be regarded as a model coronavirus for comprehensive characterization of the host cell lipid response following coronavirus infection. Glycerophospholipids and FAs of HCoV-229E-infected cells are significantly elevated and the linoleic acid to arachidonic acid metabolism axis is notably perturbed [34]. In the mitochondria, FAs are synthesized from the precursor molecules acetyl-CoA, malonyl-CoA, and malonate, and their elongation into FAs requires ATP and NADPH [35,36]. Proteomic analysis conducted on infectious bronchitis virus (IBV) coronavirus particles has identified some proteins involved in the glycolytic pathway including glyceraldehyde-3-phosphate dehydrogenase (GAPDH), aldehyde dehydrogenase 9 family, member A1 (ALDH9A1) and alpha-enolase, which had been previously identified in other viral particles including HIV-1, human cytomegalovirus (HCMV), moloney murine leukemia virus (MMLV), Kaposi's sarcoma-associated herpesvirus (KSHV) and avian influenza virus (AIV) [37–42]. Lipidomic analysis has also extended our understanding of the metabolic reprogramming following HCoV [34] and MERS-CoV infections [16,34]. Yan at al. found a considerable rearrangement of the cellular lipid profile as indicated by the accumulation of phospholipids and FAs (saturated and unsaturated) upon HCoV infection. These researchers claimed that the Coronaviridae specifically fine-tunes the host lipid profile to accomplish optimal viral replication [34]. These findings were confirmed by a recent report on the pharmacologic targeting of sterol regulatory element-binding proteins (SREBP) by AM580 (as a specific inhibitor) as a promising strategy to inhibit MERS-CoV infection [16]. Impeding the proteolytic processing of SREBP using AM580 resulted in the inhibition of multiple post-viral-entry steps, including decreased intracellular lipid droplet formation, reduced palmitoylation of viral proteins as well as reduced double-membrane vesicle (DMV) formation [16].

It has been demonstrated that PI3K/AKT/mTOR and ERK/MAPK signaling pathways have important roles in MERS-CoV infection and might represent new drug targets for therapeutic intervention [43]. PI3K-dependent trafficking of GLUT1-containing vesicles to the cell membrane, leads to increased glucose uptake and metabolism [5].

3. Metabolic interventions in COVID-19

Coronaviruses are pandemic viruses able to cause lethal lung injuries and death from acute respiratory distress syndrome (ARDS) [44]. ARDS characterized by severe hypoxemia, is generally accompanied by oxidative injury, uncontrolled inflammation, and damage to the alveolar-capillary barrier [45,46]. Enhanced oxidative stress is a key insult in pulmonary injury including ARDS, as one clinical manifestation of acute respiratory failure with considerably high morbidity and mortality [47]. Therefore, oxidative stress is a dangerous aspect of this infection. Increased extracellular oxidative stress, as a consequence of "cytokine storm", results in ARDS which is the key pathologic cause for the high mortality rate of this pandemic infection.

On such a basis, metabolic intervention in COVID-19 is suggested to follow two main goals: 1) Inhibition of virus replication 2) Inhibition of oxidative stress.

A possible strategy for achieving the first goal is: "targeting lipogenesis" that is required for virus packaging. This goal could be achieved in 3 ways a) downregulating glycolysis to inhibit pyruvate production (in a way other than inhibiting GLUT activity like GLUT1, because they are required to keep the PPP active) and entry into the TCA cycle thereby decreasing lipogenesis. Normally, glycolysis is needed to provide additional intermediates of TCA cycle for anabolic lipogenesis; b) mitochondrial targeting to decrease TCA flux; c) direct inhibition of cellular lipogenesis.

Possible strategies for achieving the second goal include: *a)* Upregulating the PPP and b) scavenging of extracellular ROS produced during infection (especially at alveolar spaces)

Regarding a) upregulating the PPP;

Intracellular oxidative stress contributes to coronavirus infectivity and increases its replication in lung epithelial cells. As demonstrated by recent studies, glucose-6-phosphate dehydrogenase (G6PD)-deficient or G6PD-knockout cells (with decreased intracellular redox power as a result of decreased NADPH) exhibit a higher susceptibility to coronavirus infection. Indeed, intracellular oxidative stress provides a proper milieu for coronavirus replication [48]. Also, these cells show a lower capacity to mount antiviral responses [49]. In fact, another reason convincing us to propose targeting of oxidative stress as a therapeutic strategy for coronavirus infection, relates to the previously published reports on the association of G6PD deficiency with coronavirus infectivity (HCoV-229E). As stated before, RNA viruses, in general, upregulate PPP which provides adequate nucleotides levels and redox power (NADPH) for sustained viral replication. Several studies, notwithstanding, made us look at this pathway (in the case of coronaviruses) somehow different and take our general view away of total beneficial effects of this pathway for coronavirus replication. As it is well-established, oxidative phase of PPP, whose key and rate-limiting enzyme is G6PD, plays a pivotal role in providing cells with sufficient redox power via NADPH production. Thus, cells lacking this key PPP enzyme have lower capacities to counteract oxidative stress. On the other hand, it has been shown that G6PD-deficient cells have a higher susceptibility to HCoV-229E (causative coronavirus of SARS) infection. In a study carried out by Wu et al. in 2008, G6PD-deficient and G6PD-knockdown cells showed much higher viral gene expression as well as viral particle production upon infection with HCoV-229E. These phenomena were associated with a higher production of oxidants, representing oxidative stress in host cells as an important factor for coronavirus infectivity. Furthermore, these researchers demonstrated that antioxidant agents could ameliorate increased viral infection of G6PD-deficient cells. This study provides the evidence that redox status of host cells plays an important role in viral infectivity [48]. Concordant with this report, these researchers in 2015 tried to delineate the underlying mechanism of this interesting phenomenon. They showed that in normal cells, viral infection triggers IκB degradation and hence NF-κB translocation that promotes antiviral responses and inhibits viral replication. But, regarding G6PD-deficient cells, they found a fall in the $NADPH/NADP^{+}$ ratio, which results in the upregulation of HSCARG protein as an NADPH sensor. This protein negatively affects the NF-κB signaling pathway, which is responsible for the expression of the antiviral genes: tumor necrosis factor-alpha (TNF-α) and GTPase myxovirus resistance 1 (MX1). Therefore, its upregulation in G6PD-deficient cells results in impaired antiviral response and, as a consequence, enhanced HCoV-229E replication [49]. PPP is the prime cellular antioxidant defense system [50]. PPP, derived from glycolysis at the first committed step of glucose metabolism, is indispensable for ribonucleotides synthesis and is also a major source of NADPH. NADPH is required for efficient scavenging of ROS. Indeed, increased PPP can be considered as a cellular mechanism to cope with intracellular oxidative stress as a

result of elevated ROS levels. Therefore, upregulating this pathway and keeping it active in this infection seems essential to reduce the detrimental effects of ROS.

Another evidence indicating the advantage of increased PPP activity in this infection is related to the autophagy process. Autophagy is suggested to play a key role in the replication of coronaviruses [51]. RNA replication of the coronavirus mouse hepatitis virus (MHV) in the host cell cytoplasm is performed on DMVs. Prentice E et al. reported that autophagy is required for the formation of DMV-bound replication complexes in MHV-infected cells; and that DMV formation markedly increased the efficiency of replication [51]. Besides, an increased autophagy has been attributed to a reduced intracellular redox power. G6PD inhibition has been shown to induce ER stress, which is responsible for autophagy flux deregulation. G6PD blockade is shown to result in a constant increase in autophagosome formation independently from mTOR status [52]. Concordantly, PPP inhibition is suggested to lead to autophagy induction. Thus, keeping this pathway active or upregulating it, as suggested in our paper, may play a role in reducing autophagy to prevent viral replication.In addition, chloroquine phosphate, which has apparent efficacy against non-severe COVID-19, restrains virus replication via blocking autophagy [53]. Chloroquine increases the pH in host cell lysosomes, and this way copes with viruses' attempts for acidifying the lysosomes. Lysosome acidification is required to form autophagosomes that cells use to eat themselves [54]. Chloroquine can restrain virus replication via blocking autophagy [55].

Nevertheless, we should keep in mind that increased NADPH as a result of upregulated PPP may be a double-deck sword as NADPH has a dual activity. In addition to serving as a fuel for the antioxidant system, NADPH can exert pro-oxidant effects by acting as a substrate for NADPH oxidases (NOXs) thereby causing lung injuries and favoring SARS-CoV-2 infectivity. On the other hand, polymorphonuclear leukocytes (PMNs) and macrophages, upon infiltrating the inflamed regions through the microvascular blood vessels, can secrete cytotoxic factors including proinflammatory cytokines and ROS. These mediators contribute to the endothelial and epithelial dysfunction leading to fluids leakage from the circulation into the interstitial space and alveoli [56]. Studies have shown that an excess of glucose entry can be diverted through the PPP, which provides additional substrates for NOX thereby resulting in a pro-oxidant environment that exacerbates inflammation [57]. Thus, increased PPP flux, through providing additional substrates for NOX enzymes, can bring about a pro-oxidant environment aggravating inflammation. Also, NOX1 and NOX2 deletion gives rise to a dramatic decrease in ROS production by macrophages [56]. Accordingly, targeting of NOX represents a proper strategy to not only decrease oxidative stress in the host cells but also mitigate the capacity of macrophages and other inflammatory cell,s for ROS production. On such a basis, it is recommended to utilize a medication that not only upregulates PPP and provides high NADPH levels to counteract oxidative stress but also concomitantly prevents NADPH entry into the mentioned pro-oxidant pathway via NOX inhibition.

As mentioned above, PPP inhibition leads to autophagy induction. Thus, keeping this pathway active or upregulating it, as suggested in this study, may play a role in reducing autophagy to prevent viral replication.

3.1. Glycolysis intervention in COVID-19

As stated, glycolysis intervention aims at lipogenesis down-regulation. Lipogenesis is required for virus packaging. Glycolysis intervention inhibits pyruvate production and entry into the TCA cycle, thereby decreasing lipogenesis. Normally, glycolysis is needed to provide additional intermediates of the TCA cycle for anabolic lipogenesis;

As in other viruses, lipids have critical roles in the life cycle of coronaviruses [34]. Lipids play crucial roles at different stages of the virus life cycle. First, lipids can act as direct receptors or entry cofactors for non-enveloped and enveloped viruses at the cell surface or the endosomes [58,59]. Second, lipids and lipid synthesis have key roles in both the formation and function of VRCs [60,61]. Third, lipid metabolism can produce the required energy for efficient viral replication [62]. Furthermore, lipids can dictate the appropriate cellular distribution of viral proteins as well as the trafficking, packaging, and release of virus particles [63,64]. Thus, the host lipid biogenesis metabolic pathways play essential roles in modulating virus propagation.

3.1.1. Glycolysis inhibitors

As outlined in Table 1 [18,65–146], our knowledge on the particular changes induced by a given virus has led to numerous strategies for targeting viral replication in cell culture and in vivo models. Therefore, given its very well-established and favorable side effect profile, ascorbic acid (vitamin C) in particular seems to be a promising compound.

3.1.1.1. Vitamin C (ascorbic acid). Vitamin C or ascorbic acid at high doses has shown alterations in metabolic pathways involving increased upstream glycolysis and PPP metabolites and decreased downstream glycolysis metabolites. Thus, this vitamin can be considered as a glycolysis inhibitor [147].

Vitamin C, by lowering viral infectivity, can be used as an inactivating agent for DNA and RNA viruses [148,149]. Additionally, ascorbic acid can detoxify viral products that cause pain and inflammation [150]. It has been shown that high dose intravenous (IV) injection of vitamin C is effective against viral infections including the common cold (rhinovirus) [151]; influenza [152,153]; zika [154]; and chikungunya [155, 156]. Oral supplementation with vitamin C (at doses over 3 g) also appears to be capable of both preventing and treating respiratory and systemic infections [157].

Two families of transport proteins, including GLUTs and sodium-dependent vitamin C transporters (SVCTs) 1 and 2, mediate vitamin C uptake. GLUTs, mainly GLUT1 and GLUT3, transport dehydroascorbic acid (DHA) into cells while SVCTs transport reduced vitamin C directly into the cells (Fig. 2) [158,159].

3.2. TCA intervention in COVID-19

The TCA cycle provides the fuel acetyl-CoA for the process of lipogenesis [46] that is crucial for sustained viral propagation. Therefore, targeting lipogenesis could pave the way for effective inhibition of viral replication.

3.2.1. TCA inhibitors

As shown in Table 2 [21,160–207], there are many Krebs cycle inhibitors with antiviral properties. Here, metformin, according to its well-established and favorable side effect profile and antiviral activity [208–215], seems to be a promising compound.

3.2.1.1. Metformin. As a drug with pleiotropic effects, metformin participates in glucose homeostasis, mostly through inhibiting liver glucose production [216]. Also, 0ne study found that metformin was significantly associated with reduced mortality from COVID-19 [217]. Metformin, by lowering the flow of glucose- and glutamine-derived metabolic intermediates into the TCA cycle leads to decreased citrate production and de novo lipid biosynthesis. Metformin acts directly on mitochondria to restrain TCA cycle activity and oxidative phosphorylation, leading cells to accept less glucose-derived carbon that favors lactic acid production [218]. Metformin brings about energetic stress in cells by inhibiting the complex I of the electron transport chain in mitochondria. This causes decreased NADH oxidation and TCA flux resulting in low levels of TCA metabolites. Therefore, metformin indirectly inhibits cellular lipogenesis (Fig. 3) [219].

On the other hand, metformin also directly hinders lipogenesis. Direct anti-lipogenic activities of metformin are mediated through inhibition of key metabolic enzymes including ATP citrate lyase (ACLY),

Table 1
Glycolysis inhibitors.

Inhibitor	Target	virus
2-DG	Phosphoglucose-isomerase	RV HIV HCMV
STO-609	CaMKK	HCMV
Compound C	AMPK	
AICAR	AMPK	
Oxamate	Lactate-dehydrogenase	KSHV
VU0359595	PLD-1	HIV
Phloretin	GLUT1	Zika virus (ZIKV)
Quercetin	GLUT1	H5N1, hepatitis C virus (HCV), HBV, influenza A virus (IAV) H1N1, DENV-2, HSV-1, polio-virus type 1, Pf-3, RSV, ZIKV, EV71, HIV
STF31	GLUT1	–
WZB117	GLUT1	–
Fasentin	GLUT1	–
Apigenin	GLUT1	ASFV, EV71, HSV-1 and HSV-2, influenza, hepatitis C virus, virus, hand, foot, and mouth disease virus
Genistein	GLUT1	B virus, HSV-1, Arenavirus, H1N1, H9N2, ASFV, human immunodeficiency type 1 virus
Oxime-based GLUT1 inhibitors	GLUT1	–
Pyrrolidinone derived GLUT1 inhibitors	GLUT1	–
DNA-damaging anticancer agents	GLUT3	–
GSK-3 inhibitors	GLUT3	–
Ritonavir	GLUT4	HIV/AIDS
Silibinin	GLUT4	hepatitis C virus, HSV-2, HBV, dengue virus, influenza virus, togaviruses (Chikungunya virus and Mayaro virus)
3-(3-Pyridinyl)-1-(4-pyridinyl)-2-propen-1-one] 3PO	PFKFB3	–
N4A	PFK2	–
YZ9	PFK2	–
PGMI-004A	PGAM1	–
MJE3	PGAM1	–
TT-232	PKM2	–
Shikonin/alkannin	PKM2	HIV type 1, AdV3, H1N1
FX11	LDHA	–
3-bromopyruvate (3BP)	hexokinase II	–
Dichloroacetate (DCA)	PDHK1	–
Diarylsulfonamide (DASA-58) (DASA)	PDHK1	–
Oxamic acid	LDH	–
NHI-1	LDH A	–
PFK158	PFKFB3	–
2-deoxyglucose (2-DG)	HK	HSV-1
Sodium fluoride (NaF)	enolase	influenza virus A/PR8/34 (H0N1), poliomyelitis virus
Acidification of blood combined with the addition of NaF and EDTA	enolase	–
sodium fluoride–potassium oxalate (NaF–KOx)	enolase	–
arsenate compounds	glyceraldehyde-3-phosphate dehydrogenase	–
Sorbinil	aldose reductase inhibitor	–
Galloflavin	lactate dehydrogenase inhibitor	–
Lonidamine	mitochondrial HK2	–
	hexokinase II	–
combination 3-BrOP and rapamycin		
combination MGCD265 and erlotinib	hexokinase II	Reactivation of hepatitis B virus after withdrawal of erlotinib
Dihydroartemisinin	pyruvate kinase M2	–
AZD8055	mTOR	–
Ethanol	hexokinase and alpha-glycerophosphate dehydrogenase	flu virus, the common cold virus, and HIV
Arenaemycin (pentalenolactone)	glyceraldehyde 3-phosphate dehydrogenase	–
Sorafenib	multikinase	Rift Valley Fever virus, HCV virus, Sindbis virus and chikungunya virus, EEEV, hepatitis B virus
1-methyl-tryptophan	Indoleamine 2,3-dioxygenase	MHV-A59, HIV, HBV, HCV, herpes, CMV
Iodoacetate	glyceraldehyde-3-phosphate dehydrogenase	Sendai virus, progeny virus, potato virus X
Iodoacetamide	glyceraldehyde-3-phosphate dehydrogenase	bovine leukemia virus, tobacco mosaic virus, Rauscher leukemia virus, RS virus, poliovirus, psittacosis virus, Cricket paralysis virus
Ascorbic Acid	blocked the energy flux	*
LY294002	PI3K	hepatitis C virus
Pt3glc and LY294002	PI3K	–
mannoheptulose	glucokinase inhibitor	–
iodoacetic acid	glyceraldehyde-3-phosphate dehydrogenase	VSV, Sendai virus, HSV-1
Malonate	succinate dehydrogenase	influenza and herpes viruses, measles virus
FTS	HIF1α expression	EMC-D virus
Lactate	PI3K	–
FK866	NAMPT	–
6-AN	G6PD	vaccinia virus
Oxythiamine	TKTL1	–
pentalenolactone	glyceraldehyde-3-phosphate dehydrogenase	HSV-1, HSV-2, Vac-IHD, Vac-DIE, NDV, VSV, WEE
Compound C	AMP-activated protein kinase	HCMV
FUT-175	complement inhibitor	–
Luteolin	HEK2	dengue virus, influenza A virus, HIV-1, Hepatitis B virus, pseudorabies virus, Epstein-Barr virus, Japanese encephalitis virus, Chikungunya virus
Quinoline 3-sulfonamides	LDHA	–

acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) complex, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) [220]. Of note, metformin hinders ROS production by suppressing NOX activity [221]. This is a key characteristic with respect to our proposed treatment protocol for COVID-19, as high cellular NADPH levels (as a result of upregulated PPP), by acting as NOX substrate, not only can result in oxidative stress and promote viral replication in the infected cell but also potentiates ROS production by the recruited inflammatory cells at the alveolar spaces contributing to ARDS.

4. Inhibition of COVID-19 related oxidative stress

Acute organ failure, particularly pulmonary failure (ARDS), is the major mechanism for COVID-19 related fatality [222,223]. Substantially increased oxidative stress owing to the rapid release of cytokines and free radicals, etc. is the hallmark of ARDS that results in cellular injury, organ failure, and death [44]. Therefore, early intake of high

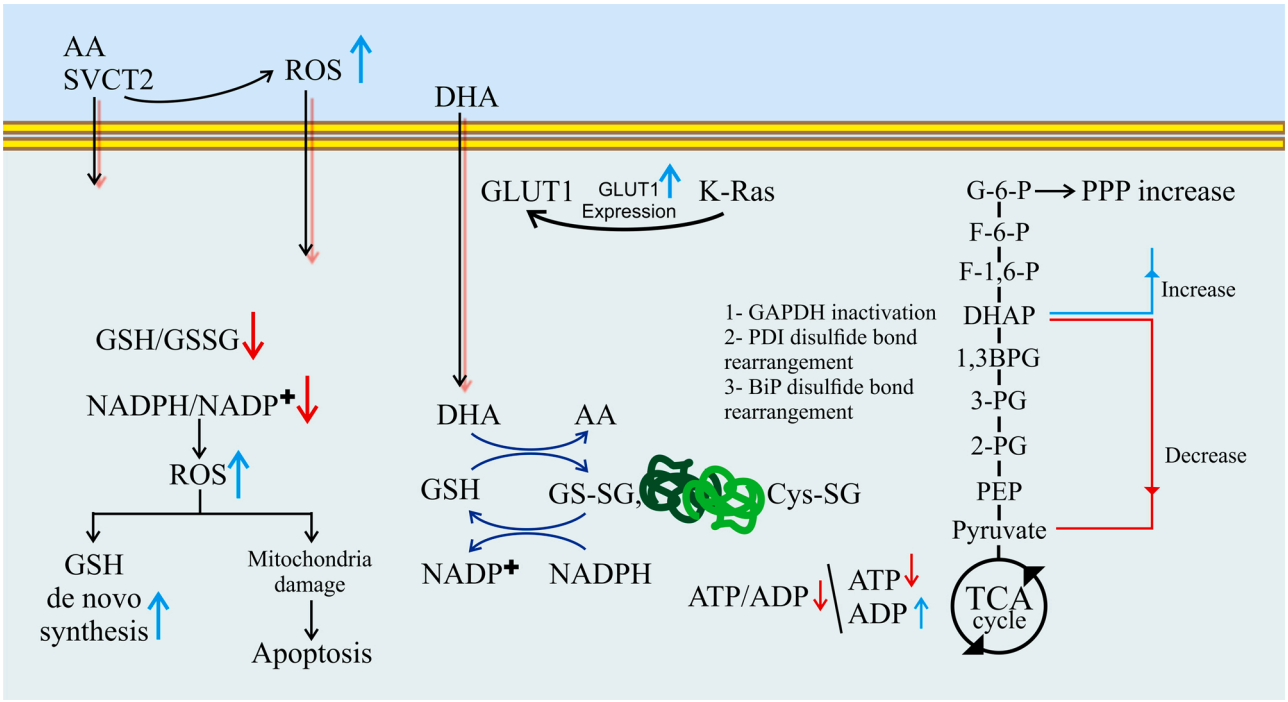

Fig. 2. Effects of vitamin C on intracellular redox metabolism and glucose metabolism.

dose antioxidants, especially vitamin C, plays a crucial role in the management of such patients. Hence, in the case of coronavirus epidemic, all those in the leadership and those providing direct assistance patients are recommended to rapidly and bravely apply high dose IV vitamin C.

Increased oxidative stress, as a consequence of "cytokine storm," results in ARDS as the key pathologic cause for the high mortality rate of this pandemic viral infection. Cytokine storm-induced ARDS is the key pathoenic event responsible for the death of these patients [44]. IV vitamin C is suggested to effectively cope with cytokine storm-induced oxidative stress (Fig. 4) [224].Vitamin C is a pivotal component of the antioxidant system in cellular response [225].As a matter of fact, high dose IV vitamin C has been applied clinically successfully in viral ARDS as well as in influenza. Fowler et al. reported a 26-year-old woman developing viral ARDS due to rhinovirus and enterovirus-D68 [226] Hemila et al. reported that vitamin C makes ICU stay shorter according to their 2019 meta-analysis of 18 clinical studies published in the journal Nutrients [227]. In their report, vitamin C shortened ICU stay by 97.8 % in a subgroup of 1766 patients. Marik and colleagues reported their use of IV vitamin C in 47 sepsis ICU cases. They found a considerable decrease in the mortality rate in the group of patients receiving IV vitamin C [228].

In patients receiving mechanical ventilation, dietary antioxidants (vitamin C and sulforaphane) have been shown to decrease oxidative stress-induced acute inflammatory lung injury [229]. Other antioxidants (like curcumin) have also shown promising anti-inflammatory potentials in pneumonia [230].

Based on these reports, targeting the recalcitrant COVID-19 related oxidative stress with high dose antioxidants (like vitamin C) seems a logical step in the immediate management of this catastrophic pandemic, without the lengthy waiting for pathogen-specific drugs and vaccines. Also, metformin has been shown to decrease ROS and nitric oxide (NO) levels and increase the antioxidant system, such as superoxide dismutase (SOD) [231].

Vitamin C serves as a mild pro-oxidant capable of producing free radicals and, as a result, induces mitochondrial biogenesis. Mitochondrial biogenesis enhances the metabolic enzymes needed for glycolysis and oxidative phosphorylation, and hence creates a greater mitochondrial metabolic capacity. As shown by a study exploring the effects of azithromycin and doxycycline on the mitochondrial biogenesis, low doses of these antibiotics were able to inhibit mitochondrial biogenesis [232]. Also, azithromycin and doxycycline exhibit antiviral activities [233–241].

5. Conclusion

The pandemic outbreak of the novel coronavirus SARS-CoV-2 in 2020 vigorously necessitates as urgent finding of effective therapeutic agents as possible [242]. At present, there is no definite and effective treatment for SARS-CoV-2 infection. Acute organ failure, especially pulmonary failure (acute respiratory distress syndrome or ARDS), is the key pathogenic mechanism governing SARS-CoV-2 fatality. Significantly increased oxidative stress due to the rapid release of free radicals and cytokines, etc. is the hallmark of ARDS, resulting in cellular injury, organ failure, and finally death [222,223]. Also, according to the recent publications concerning the higher susceptibility of G6PD-deficient cells to coronavirus (HCoV-229E) infectivity, oxidative stress in host cells provides a proper milieu for coronavirus replication [48]. Therefore, reducing ROS levels in patients with COVID-19 seems a therapeutic strategy against this disease. Another therapeutic strategy is to prevent virus replication. A therapeutic approach incorporating both of these aspects can be considered optimal treatment.

Vitamin C, with its antioxidant properties, is known to reduce ROS. But can it stop the virus replication?

We propose the use of vitamin C for COVID-19 treatment to not only directly counteract the deleterious and dangerous effects of augmented oxidative stress responsible for ARDS in the extracellular space (alveolar space), but also hinder glycolysis and instead upregulate PPP and intracellular NADPH for creating a higher cellular redox status with the aim of lowering SARS-CoV-2 infectivity, as oxidative stress has been elucidated to promote coronavirus infectivity. Also, due to the very recent report on the autophagy-inducing effect of G6PD blockade that causes increased viral replication, we assume that PPP upregulation is likely to cope with SARS-CoV-2 replication through this autophagy-mediated mechanism, too. But further researches in the future remain to fully shed light on this facet of coronavirus infection. Early use of high

Table 2
TCA inhibitors.

Inhibitor	Enzymes	VIROUS
H_2O_2	Aconitase, α-Ketoglutarate dehydrogenase	rabies virus, plant virus,, influenza A and B, rhinoviruses 1A, 1B, and type 7, adenovirus types 3 and 6, adenoassociated virus type 4, myxoviruses, respiratory syncytial virus strain Long, and coronavirus strain 229E
AG-120 (Ivosidenib)	IDH1	–
AG-221	IDH2	–
Novartis-530	IDH1	–
FX 11	LDH-A	–
Dichloroacetate (DCA)	PDK	–
miR-26a	PDHX	Influenza A virus, Feline Herpesvirus 1, respiratory syndrome virus
miR-146b-5p	PDHB	human papilloma virus 16, dengue virus (DENV)
miR-370	PDHB	hepatitis B virus, Japanese encephalitis virus
miR-137	ASCT2	–
miR-183	IDH2	vesicular stomatitis virus (VSV)
miR-181a	IDH1	LCMV
fumarate	PHD2	–
succinate	PHD2	–
2-hydroxyglutarate	α-KG-dependent dioxygenases	–
Alloxan	mitochondrial aconitase, Succinic dehydrogenase	–
Thioredoxin	succinate dehydrogenase and fumarase & ATP-citrate lyase	H9N2 avian influenza virus
6-diazo-5-oxo-L-norleucine	glutaminolysis	mumps and vesicular stomatitis viruses, human parainfluenza virus type 2 (HPIV-2), NSV
CB-839	GLS	adenovirus, HSV-1, and influenza A
CPI-613	PDH and KGDHC	–
enasidenib (AG-221)	IDH2	–
AG-881	IDH1 and IDH2	–
AG-221	IDH2-R140 and IDH2-R172	–
Oxalomalate	oxoglutarate dehydrogenase, aconitate hydratase and isocitrate dehydrogenase	–
gamma-hydroxy-alpha-oxoglutarate	oxoglutarate dehydrogenase, aconitate hydratase and isocitrate dehydrogenase	–
glyoxylic acid	pyruvic oxidase and tentatively as α-oxoglutaric oxidase and succinic oxidase	–
Fluoroacetate	aconitase	influenza virus
3-BrPA	isocitrate dehydrogenase, α-ketoglutarate dehydrogenase and succinate dehydrogenase	–
Sodium malonate	succinate dehydrogenase	–
Sodium arsenite	pyruvate dehydrogenase	WT or NS1 mutant viruses, PEDV
Metformin and phenformin	mitochondrial complex 1	*
D-malate	Fumarase	–
Citrate	Fumarase	–
D-tartrate	Fumarase	hepatitis C virus NS5A
L,a-hydroxy-beta-sulfopropionate	Fumarase	–
Maleate	Fumarase	Influenza Viruses, Dengue virus
mesaconate	Fumarase	–
Transaconitate	Fumarase	–
Succinate	Fumarase	–
Malonate	Fumarase	–
Adipate	Fumarase	–
Glutarate	Fumarase	–
Glycine	Fumarase	–
Arsenoso compounds	Pyruvic oxidase, choline dehydrogenase, succinic dehydrogenase	–
Hematin	Succinic dehydrogenase	–
Cyanide	succinate dehydrogenase	–
Copper ions	Succinic dehydrogenase	influenza A virus
Maleic acid	Succinic dehydrogenase	aphthous fever virus
Sodium diethyldithiocarbamate (DDC)	Succinic dehydrogenase	HIV and AIDS

dose antioxidants, especially vitamin C, therefore, plays a key role in the management of these patients. In a study, modest quantities of supplemental vitamin C (200 mg of vitamin C daily) led to an 80 % reduction in death among severely ill, hospitalized respiratory disease patients [227]. Infants with viral pneumonia administered with vitamin C have shown reduced mortality [243]. In a subgroup of 1766 patients, moderate doses of vitamin C shortened ICU stay by 97 % [227]. The major danger with SARS-CoV-2 infection is disease progression to SARS and pneumonia. Since the 1940s, medical doctors have successfully used vitamin C against viral pneumonia [244].

To replicate, RNA viruses upregulate both glycolysis and glycogenolysis, providing their host cells with TCA intermediates required for anabolic lipogenesis. The novel emerged coronavirus, SARS-CoV-2, which has thus far spread from China throughout the world with fatal outcomes, is an RNA virus as well [6]. Also, evidence points to a higher PPP flux following RNA virus infections [245], as is the case in the rhinovirus infection, which results in the production of higher nucleotide levels supporting viral replication. On such a basis, inhibition/modulation of these metabolic pathways could contribute to the inhibition of viral replication. But, concerning coronaviruses, direct and clear data on the exact status of this metabolic pathway in the infected cell is scarce. Rather, recent data highlights the contributing role of intracellular oxidative stress to coronavirus infectivity, further bringing into question the exact role/status of this pathway during coronavirus infection. From this point of view, PPP upregulation, by providing higher NADPH levels and potentiating intracellular redox power, is suggested to impair coronavirus replication. But how does SARS-CoV-2 itself manipulate this pathway in the lung epithelial cells? The response hides behind the meticulous evaluation of the PPP following SARS-CoV-2 infection warranting more in-depth investigations in this regard. However, based on the reported pathogenic role oxidative stress plays in promoting coronavirus infection, we suggest upregulated PPP in the infected host cells as a therapeutic mechanism.

Vitamin C inhibits glycolysis, which is a metabolic pathway used by cells to convert glucose into energy. As stated, RNA viruses for sustained replication increase glycolysis and glycogenolysis, thereby providing TCA intermediates required for anabolic lipogenesis [245]. Thus, despite the blockade of the glycolysis pathway by vitamin C, other pathways linked with the TCA cycle (like catabolism of some amino acids) are still open. Therefore, in addition to vitamin C (which indirectly downregulates the TCA cycle), inhibition of viral replication requires another substance that can block the TCA cycle.

We propose upregulated PPP could exert antiviral effects in SARS-CoV-2 infection. Since increased levels of ROS play an important role in this viral infection, an increased flux of PPP in this infection is regarded as a therapeutic strategy. RNA virus-infected cells immediately

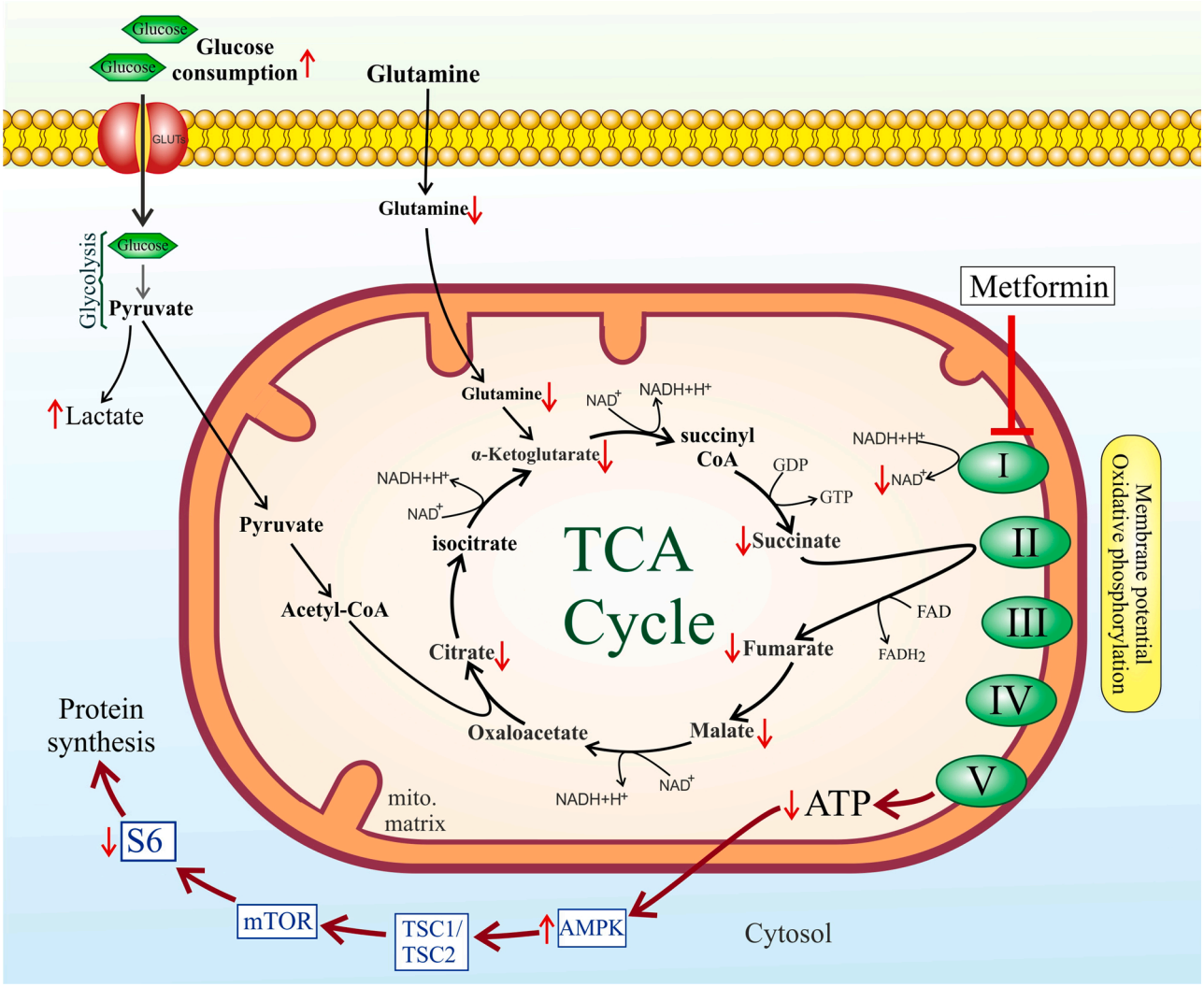

Fig. 3. TCA cycle intervention by metformin.

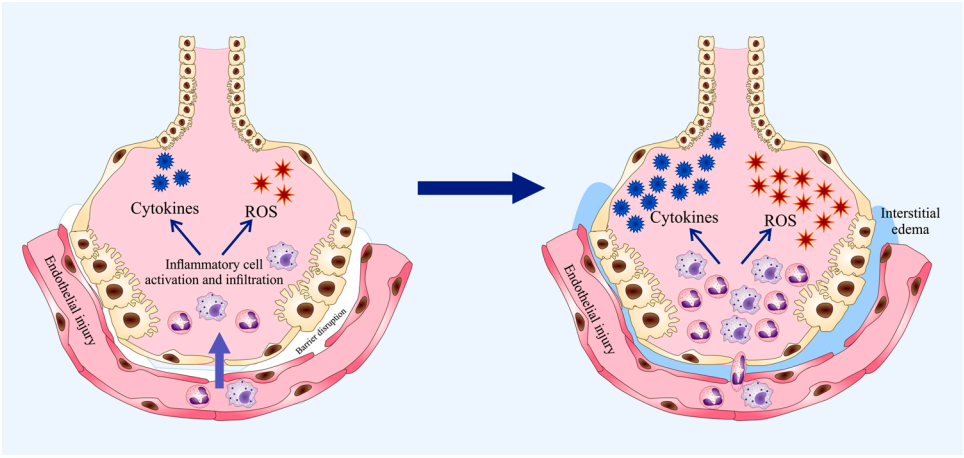

Fig. 4. Impaired function of alveolar epithelium and microvascular endothelium in ARDS. Microvascular blood vessels allow elevated infiltration of polymorphonuclear leukocytes (PMNs) and macrophages into the inflamed region followed by increased release of cytotoxic factors including proinflammatory cytokines and ROS. These released mediators contribute to the endothelial and epithelial dysfunction leading to fluids leakage from the circulation into the interstitial space and alveoli. Combined, these events result in pulmonary edema and impaired gas exchange.

upregulate glucose uptake in a PI3K-dependent manner. In parallel, infected cells augment the expression of the PI3K-regulated GLUT1 [17]. The point to consider in blocking the glycolysis pathway is to use an inhibitor that does not inhibit GLUT1, because we need this transporter to keep the PPP active. 2-deoxyglucose (2-DG) appears to be a promising compound in this regard, given its well-established and favorable side effect profile and antiviral properties. 2-DG has no antioxidant property compared to vitamin C. Rather, it induces oxidative stress [246] Therefore, vitamin C as an antioxidant and an inhibitor of the glycolysis pathway with concomitant effects on PPP upregulation, could be a good choice for the treatment of this viral infection.

As the PPP upregulates, the production of ribonucleotides required

for virus replication increases. Since the virus relies on host cell lipogenesis for its replication, targeting lipogenesis is speculated to inhibit virus replication even in the presence of large amounts of ribonucleotides. In this regard, inhibition of lipogenesis via Krebs cycle blockade seems conceivable. As mentioned above, TCA cycle blockade is required for the inhibition of viral replication. Metformin is introduced for this purpose. Metformin, not only decreases mitochondrial TCA cycle intermediates but also directly inhibits lipogenesis [219,220]. Since metformin suppresses NOX activity, its intake would cicumvent the potential hazardous impacts of high intracellular NADPH levels (due to upregulated PPP) in terms of generating higher ROS (contributing to the detrimental function of proinflammatory cells) and creating intracellular oxidative stress (contributing to increased SARS-CoV-2 infectivity in the host cell), as well. On the other hand, vitamin C is a mild pro-oxidant. Therefore, it can produce free radicals and, as a result, induces mitochondrial biogenesis. This can act in favor of SARS-CoV-2 replication by providing the cell with a higher number of factories in charge of TCA cycle flux and consequently lead to increased lipogenesis. To avoid the effect, we propose a strategy to both inhibit mitochondrial biogenesis and hamper mitochondrial protein translation. The use of azithromycin or doxycycline (or both) at low doses (that spares antibiotic resistance) has been shown to prevent mitochondrial biogenesis. Alsoas off-target side effects, azithromycin and doxycycline can inhibit large and small mitochondrial ribosomes, respectively [232]. Additionally, these antibiotics also possess antiviral activities [233–241].

A combination of vitamin C, metformin and doxycycline/azithromycin, is suggested to serve as an effective treatment for this infection. As these compounds are non-toxic, we hope that this therapeutic strategy can be applied with minimal side effects. It is worth mentioning that, applying this strategy for the treatment of stormy and fatal outbreaks of this pandemic virus in the world is still in the hypothesis level, and final corroboration is in dire need of supportive clinical evidence.

Declaration of Competing Interest

The authors report no declarations of interest.

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