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Metabolic alterations upon SARS-CoV-2 infection and potential therapeutic targets against coronavirus infection

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The coronavirus disease 2019 (COVID-19) caused by coronavirus SARS-CoV-2 infection has become a global pandemic due to the high viral transmissibility and pathogenesis, bringing enormous burden to our society. Most patients infected by SARS-CoV-2 are asymptomatic or have mild symptoms. Although only a small proportion of patients progressed to severe COVID-19 with symptoms including acute respiratory distress syndrome (ARDS), disseminated coagulopathy, and cardiovascular disorders, severe COVID-19 is accompanied by high mortality rates with near 7 million deaths. Nowadays, effective therapeutic patterns for severe COVID-19 are still lacking. It has been extensively reported that host metabolism plays essential roles in various physiological processes during virus infection. Many viruses manipulate host metabolism to avoid immunity, facilitate their own replication, or to initiate pathological response. Targeting the interaction between SARS-CoV-2 and host metabolism holds promise for developing therapeutic strategies. In this review, we summarize and discuss recent studies dedicated to uncovering the role of host metabolism during the life cycle of SARS-CoV-2 in aspects of entry, replication, assembly, and pathogenesis with an emphasis on glucose metabolism and lipid metabolism. Microbiota and long COVID-19 are also discussed. Ultimately, we recapitulate metabolism-modulating drugs repurposed for COVID-19 including statins, ASM inhibitors, NSAIDs, Montelukast, omega-3 fatty acids, 2-DG, and metformin.

INTRODUCTION

In the 21st century, coronavirus infections have become major global challenges not only to public health, but also to government managements. Just in the last two decades, we have experienced three pandemic outbreaks caused by ß-coronavirus infections. Coronaviruses are enveloped viruses containing an ~30 kb positive-sense single-stranded RNA [(+) ssRNA] genome.[1] Coronaviruses transmit among different species, including humans, livestock, and wild animals. An epidemic caused by SARS-CoV outbroke in China in 2002-2003, culminating in 774 reported casualties. Middle East respiratory syndrome coronavirus (MERS-CoV) accounts for another global outbreak in 2020 with over 800 associated deaths.[2] Since December 2019, coronavirus disease 2019 (COVID-19) has caused a global pandemic with symptoms of pneumonia, nausea, fever, and respiratory system impairment.[3,4] COVID-19 is caused by a novel pathogen, namely severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Since 2019, COVID-19 has brought unprecedented casualties and socioeconomic burden.[4,5]

Most COVID-19 cases are asymptomatic or mild. However, some patients have courses characterized by a generalized inflammatory state causing tissue injury in multiple organs and ARDS with a global mortality rate of 3.4%.[6] Patients with hypertension, diabetes, and cardiovascular diseases have a higher risk of mortality.[7,8] Hitherto, due to a paucity of validated modalities or vaccines, COVID-19 remains a horrendous threat worldwide. Despite enormous scientific efforts that have been dedicated to

SARS-CoV-2, the deep layers of SARS-CoV-2 biology and pathogenesis are not yet well understood.

The envelope (E), membrane (M), and spike (S) proteins together comprise the outer shield of SARS-CoV-2; while the core of SARS-COV-2 consists of viral genomic RNA condensed by nucleocapsid (N) protein. The viral genome RNA encodes non-structural proteins (NSPs), structural proteins (E, M, S, and N) and accessory proteins. NSPs are functional in viral RNA replication, protein synthesis, and regulating intracellular signaling pathways.[9,10] NSPs also play crucial roles in attenuating host innate immunity to facilitate the escape from host defense and initiate inflammatory response.[11] S gives rise to the corona shape of the surface and mediates host receptor recognition and viral entry. SARS-CoV-2 specifically recognizes and attaches human angiotensin-converting enzyme 2 (ACE2) for entry via S protein.[12,13] E mediates virus assembly, membrane scission, and budding, playing a pivotal role in virus replication and intercellular transmission.[14] M is the most abundant protein in the envelope that directs the assembly process through interaction with the other structural proteins.[15] N directly binds with viral RNA, serving as capsulation to protect viral RNA from cytoplasmic immune surveillance and to mediate nucleoprotein complex assembly.[16–18]

The life cycle of coronaviruses generally includes the following stages (as shown in Fig. 1): host cell receptor specific engagement with S protein[19]; viral uptake by endocytosis or membrane fusion[13]; uncoating and viral RNA synthesis in replication organelles[20,21]; progeny virions assembly to mature virions;

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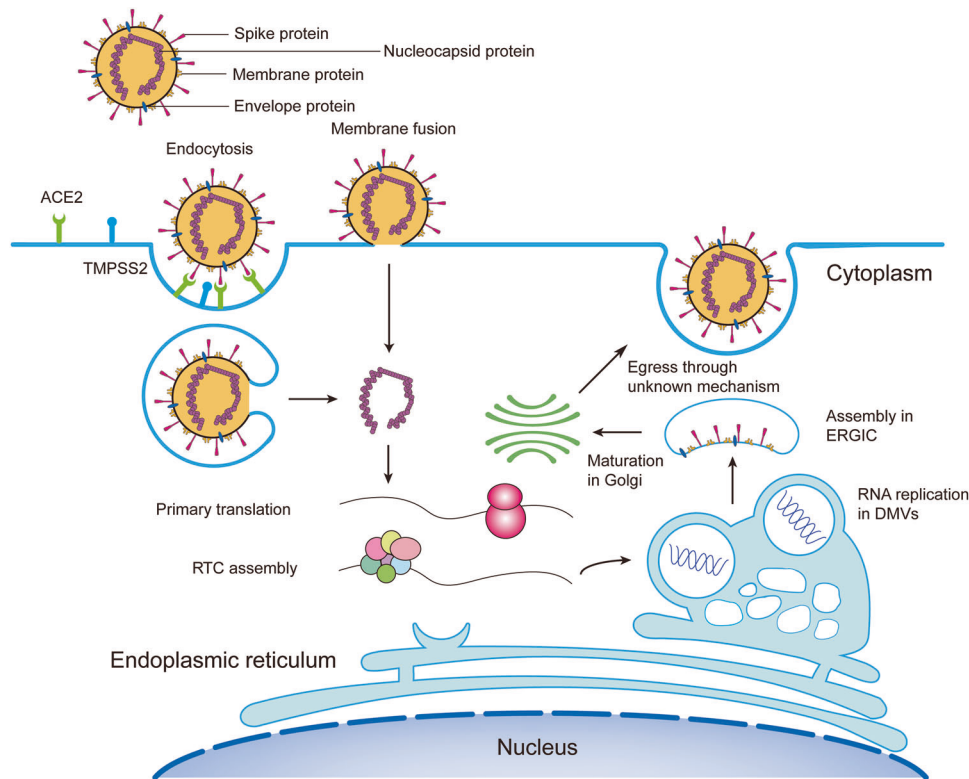Chen et al.

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Fig. 1 The life cycle of SARS-CoV-2. The life cycle of SARS-CoV-2 includes the following stages: receptor recognition via S protein; viral entry through the endocytosis pathway or the membrane fusion pathway; replicative transcription complex formation; viral RNA replication in DMVs; virion assembly in ERGIC; virion maturation in Golgi; egress through an unknown pathway

ultimate release by unknown mechanism.[3] Following viral entry by membrane fusion or endocytosis, the release and uncoating of viral genomic RNA, together with NSPs, subject to translation and formation of replication and translation complex (RTC). In the replication stage, viral genomic RNA is coated by double-membrane vesicles (DMVs), which are derived from the endoplasmic reticulum (ER).[22] DMVs provide a microenvironment to protect the viral genome and to facilitate viral RNA synthesis.[23,24] DMVs have a pore to connect with the cytoplasm for material exchange while shielding viral RNA from intracellular immune surveillance.[25] In the assembly stage, newly produced viral RNA and NSPs are subsequently incorporated into virions at the cytoplasmic side of the ER-to-Golgi intermediate compartment (ERGIC).[26,27] After being transported to Golgi, coronaviruses are further modified and assembled, giving rise to the morphology of mature virions. Ultimately, virions egress from the host cell by exocytosis. As for the mechanism for viral egress, debates still exist. It was initially postulated that SARS-CoV-2, similar to other enveloped viruses, hijacks the biosynthetic secretory pathway for its exit. However, recent research discovers that coronaviruses including SARS-CoV-2 use lysosome for egress instead of hijacking the biosynthetic secretory pathway.[28] Until now, the egress mechanism of coronaviruses has not been determined yet.[27,29]

Lipid metabolism is indispensable in providing energy and material, maintaining homeostasis, regulating immune response, and relaying signals. Many viruses were reported to rewire host cellular lipid metabolism to create replication compartments.[30–34] Lipid droplet (LD), a cellular organelle for lipid storage, was reported to be closely associated with cellular antiviral innate immunity.[35,36] Lipid accumulation was observed in the lungs of COVID-19 patients and cells infected by SARS-CoV-2, colocalizing with N protein.[37,38] Significant lipid pattern alterations were demonstrated by Lipidomic analyses of plasma from COVID-19 patients, and the lipid pattern was shown to correlate with disease severity and progression.[39,40]

Glucose metabolism is another network that regulates a series of physiological alterations. Aside from providing energy and material for cells, glucose metabolism is also associated with virus infection, immunity, tumorigenesis, homeostasis, and so forth.[41–47] More importantly, it is supported by clinical evidence that diabetes mellitus, which is characterized by an impaired capability to control blood glucose, is a major risk factor predisposing to severe COVID-19.[7,48,49] A retrospective study shows that well-controlled blood glucose is associated with markedly lower mortality rates. On the contrary, patients with type 2 diabetes (T2D) or dysregulated blood glucose have poor outcomes.[50] Analysis of single-cell RNA-sequencing data in bronchoalveolar lavage fluid immune cells reveals that enhanced glycolysis is the most important metabolic feature of all immune cells in COVID-19 patients.[51] The relationship between dysregulated blood glucose profile and COVID-19 is bidirectional. Infection by SARS-CoV-2 could also worsen the condition of type 2 diabetes patients.[52,53]

Considering the huge socioeconomic damage caused by coronaviruses, it is an urgent need to develop effective therapeutic interventions for the next outbreak. A more profound comprehension of host metabolic alterations and their association with coronaviruses will prompt us to understand more about COVID-19 pathology and promote antiviral drug development. This review aims to generalize and discuss current findings about the role of host metabolism in SARS-CoV-2 infection.

Virus entry
Apart from ACE2, other host receptors including lectins, DC-SIGN, L-SIGN, and AXL, also serve as alternative entry sites of SARS-CoV-2.[54–56] S protein trimers recognize and bind to cell receptor ACE2 with its S1 domain. Then S protein is cleaved by

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host transmembrane serine protease TMPRSS2 at the S2' site.[57] The anchored S2 domain is activated to trigger viral and host lipids bilayer fusion, releasing the viral ribonucleoprotein complex into the cell.[58–60] In addition to the membrane fusion pathway, endocytosis is also hijacked for SARS-CoV-2 entry.[61,62] The endocytosis pathway mediates the trafficking of SARS-CoV-2 to the late endosome/lysosome, in which proteases (such as cathepsin L) prime S protein to initiate membrane fusion.[63,64]

Increasing evidence supports the critical role of *lipid rafts* in SARS-CoV-2 infection. Lipid rafts are located at cell membranes, they are microdomains enriched in lipid molecules including cholesterol and sphingolipids. Lipid rafts are involved in a variety of physiological processes.[65] Lipid rafts are also proposed as important for the entry of other coronaviruses by providing a platform for entry receptors. Lipid rafts are suggested to be a promising therapeutic target.[66–68] From a mechanistic perspective, lipid rafts provide platforms for membrane receptors involved in viral entry of SARS-CoV-2.[69] SARS-CoV-2 entry can be reduced by disturbing lipid rafts. ACE2 colocalizes with well-established raft proteins caveolin-1, flotillin-2, and ganglioside GM1 in Vero E6 cells.[70,71] However, either endogenous ACE2 in Vero E6 cells or the transiently expressed ACE2 in CHO cells is not enriched in lipid rafts.[72,73] The controversial results might be caused by different experimental methods. How and which receptors are recruited to the lipid rafts requires further investigation.

Changes in cholesterol levels disrupt *lipid rafts* and the receptors attached.[74] SARS-CoV-2 spike-bearing pseudovirus infection is associated with cholesterol-rich lipid rafts.[75] Accordingly, Cholesterol-25-hydroxylase, an interferon-stimulated gene (ISG) that triggers cholesterol trafficking from the plasma membrane to ER, inhibits SARS-CoV-2 entry by depriving accessible cholesterol at the plasma membrane. More importantly, the entry inhibition can be restored by replenishing soluble cholesterol to the cells.[76] Furthermore, lipid rafts are also proposed to promote viral entry through the endocytosis pathway. SARS-CoV-2 internalization is mediated through a lipid raft-dependent endocytic pathway, but which endocytosis pathway is practically responsible for SARS-CoV-2 entry entails further investigations.[75] In some enveloped viruses, infection causes fusogenic viral protein displayed on the cell membrane, which allows adjacent cells to fuse and form multinucleated syncytia.[77,78] Syncytia formation is also observed in SARS-CoV-2 infected cells or lungs of deceased patients.[79,80] Syncytia formation indicates that SARS-CoV-2 has an ability of cell-to-cell transmission, allowing the virus to avoid contact with antibody.[81] Of note, it is evident that cell-to-cell transmission through the formation of channels or syncytia requires intact lipid rafts.[82] In addition, S protein-mediated membrane fusion and syncytia formation requires cholesterol involvement.[80] Hence, it is reasonable to deduce that lipid rafts are also involved in syncytia formation during SARS-CoV-2 infection.

Intriguingly, S protein can directly interact with *cholesterol*. A study identified putative cholesterol recognition amino acid consensus motifs in SARS-CoV-2 S protein. Antibodies blocking the cholesterol-binding site of S protein significantly curbed viral entry.[83] The interaction between S protein and high-density lipoprotein (HDL) has been interrogated. SR-B1 is an HDL receptor located on the cell membrane that drives the cellular uptake of cholesteryl esters and other lipid components of HDL.[84] S protein directly binds with SR-B1-bound HDL and captures lipid materials from HDL. Genetic depletion of SR-B1 curbs SARS-CoV-2 pseudovirus entry.[83] Another study also demonstrated that S protein can remove lipid components from HDL. Co-culture of HDL with S protein altered the function of HDL to exchange lipids from model cellular membranes.[85]

Although *cholesterol* on cell membrane facilitates viral entry, the role of intracellular cholesterol in SARS-CoV-2 infection is more complicated. Two independent genetical screens by CRISPR libraries identified genes in cholesterol metabolism as essential for SARS-CoV-2 infection, including sterol-regulatory element-binding protein (SREBP-2), SREBP cleavage activating protein (SCAP), low-density lipoprotein receptor (LDLR), and Membrane-Bound Transcription Factor Peptidase, site 1 and 2 (MBTPS1 and MBTPS2). Treatment of amlodipine, a calcium-channel antagonist that increases intracellular cholesterol levels, significantly inhibited SARS-CoV-2 infection.[86,87] In addition to facilitating viral entry, it is likely that cholesterol metabolism also affects SARS-CoV-2 infection in other stages of its life cycle. Future studies on the interplay between SARS-CoV-2 and cholesterol metabolism are warranted.

Many viruses including ebola virus (EBOV), human immunodeficiency virus type I (HIV-1), hepatitis C virus (HCV), and simian virus 40 (SV40) are reported to employ *sphingolipids* for cell membrane attachment.[88–91] The sphingolipid metabolism pathway is also manipulated for SARS-CoV-2 entry (Fig. 2). Sphingolipids and their metabolites together comprise a complex network of signaling in a series of physiological processes, including maintaining cellular structure, relaying signals, and modulating enzymatic activity.[92] Elevated sphingolipid levels stimulated by SARS-CoV-2 were observed in cells and mice serum. Analysis of COVID-19 patient serum samples indicated a distinct alteration in sphingolipid profiles. The result shows a progressive increase in dihydrosphingosine, dihydroceramides, ceramides, sphingosine, and a decrease in sphingosine-1-phosphate (S1P).[93,94] Acid sphingomyelinase (ASM) catalyzes the hydrolysis of sphingomyelin to ceramide and phosphorylcholine. Increased circulating activity of ASM and derangement of sphingolipids were observed in COVID-19 patients. The increase of ASM activity accurately distinguishes the patient cohorts undergoing intensive care from healthy controls.[94] Among the various sphingolipids, the impact of ceramide and sphingosine on SARS-CoV-2 entry is prominent. Ceramide is converted from sphingomyelin by ASM or synthesized de novo from palmitoyl CoA and serine. Several ASM inhibitors including antidepressants (Amitriptyline, Imipramine, Fluoxetine, Sertraline, and Escitalopram) or ASM-knockout potently hindered SARS-CoV-2 entry in vivo. The suppressive effect is exerted partially via an impaired surface ceramide level since the replenishment of exogenous ceramide restored SARS-CoV-2 entry.[95] Ceramide-enriched domain formed by released ceramide on the cell surface promoted SARS-CoV-2 entry.[96,97] Furthermore, SARS-CoV-2 induced ACE2 clustering in ceramide-enriched domains on the membrane of nasal epithelial cells isolated from healthy donors. Ambroxol, an ASM inhibitor, potently suppressed ACE2 clustering on the cell membrane and reduced viral uptake by the epithelial cells.[98] Fluoxetine, amiodarone and imipramine exhibited profound inhibitory activity on SARS-CoV-2 entry. This study indicated that further than removing membrane ceramide, ASM inhibitors can induce endolysosomal cholesterol accumulation and dysregulated acidification, hence blocking SARS-CoV-2 entry via the endosomal pathway.[99] It is noteworthy that C16 ceramide presumably plays a central role in promoting SARS-CoV-2 entry since an exogenous supplement of C16 ceramide restored SARS-CoV-2 infection under ASM inhibitors treatment.[98] The precise role of ceramide needs to be further defined.

Sphingosine derives from ceramide by ceramidase catalyzation or from S1P by S1P phosphatase catalyzation. Sphingosine plays quite a contrary role to ceramide: while ceramide promotes SARS-CoV-2 entry, sphingosine impedes it. Sphingosine binds with membrane ACE2, thereby blocking the interaction between ACE2 and S protein, consequently inhibiting SARS-CoV-2 entry.[100] The above findings provide reference for therapeutic interventions since drugs interfering with sphingolipids metabolism pathway like antidepressants are well-tolerated and extensively applied in clinic.[101]

Glycolipids are essential for SARS-CoV-2 entry, especially sialylated glycolipids. Monosialylated gangliosides have a strong

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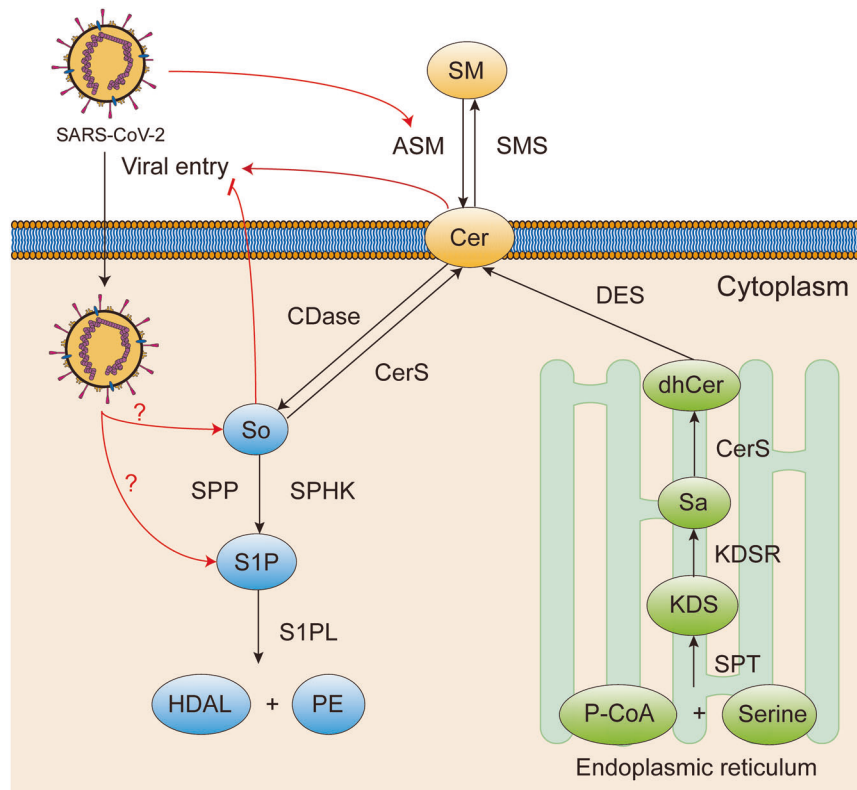Chen et al.

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Fig. 2 The sphingolipids metabolism pathway. Sphingomyelin on the plasma membrane can be converted to ceramide by sphingomyelinase. Ceramide can also be synthesized de novo from palmitoyl CoA and Serine or synthesized from sphingosine by ceramide synthase. SM Sphingomyelin, Cer ceramide, So Sphingosine, S1P Sphingosine 1-phosphate, HDAL Hexadecenal, PE Phosphorylethanolamine, dhCer dihydroceramide, Sa Sphinganine, KDS 3-ketodihydrosphingosine, P-CoA Palmitoyl-CoA, ASM Acid sphingomyelinase, SMS Sphingomyelin synthase, CDase Ceramidase, CerS Ceramide synthase, SPP S1P phosphatase, SPHK Sphingosine kinase, S1PL S1P lyase, DES dihydroceramide Δ4-saturase, KDSR 3-ketodihydroshpingosine reductase, SPT Serine palmitoyltransferase

binding affinity with the receptor binding domain (RBD) of S protein. GENZ-123346 is an inhibitor of UDP-glucose ceramide glycosyltransferase (UGCG) that can deplete glycolipids from the cell membranes. GENZ-123346 treatment caused profoundly attenuated SARS-CoV-2 entry in vitro. Consistently, UGCG ablation by CRISPR/Cas9 also curbed SARS-CoV-2 infection.[102] Chloroquine binds with sialic acids and gangliosides with a higher affinity than S protein. Treatment of chloroquine or its derivative, hydroxychloroquine, actively reduced SARS-CoV-2 S protein binding with gangliosides and exhibited potent antiviral activity.[103,104] Moreover, chloroquine and hydroxychloroquine can be incorporated into endosomes, resulting in an increase of endosomal pH and prevention of viral entry via endocytosis.[105] Results from in vitro experiments further confirmed the antiviral effect of chloroquine and hydroxychloroquine against SARS-CoV-2.[58] Nevertheless, the clinical use of chloroquine or hydroxychloroquine is still controversial due to insufficient clinical data. Although some clinical studies showed the benefit of chloroquine and hydroxychloroquine, they are not completely reliable because they are non-peer-reviewed, unblinded, or non-randomized.[106] Besides, the cardiotoxicity of chloroquine should also be taken into consideration since cardiovascular disorders are also major complications of COVID-19. The European Medicines Agency has refused to approve chloroquine for COVID-19. However, several clinical trials in China proved the efficacy of chloroquine and hydroxychloroquine.[107–109] The use of chloroquine for the treatment of COVID-19 has been added to the guideline (version 6) in China.

Intriguingly, a recent report identified the bile acid receptor *farnesoid X receptor (FXR)* as a direct regulator of ACE2 expression. The presence of the FXR responsive element was uncovered in the ACE2 promoter region. Upon activation, FXR directly binds with

the ACE2 promoter, confirmed by chromatin immunoprecipitation. Bile acid chenodeoxycholic acid (CDCA) is the major agonist of FXR. Treatment of CDCA markedly upregulated ACE2 expression and enhanced SARS-CoV-2 infection in vitro, in vivo, and in organoids in an FXR-dependent manner. A clinically approved FXR inhibitor, ursodeoxycholic acid (UDCA), significantly downregulated ACE2 expression and exhibited potent antiviral activity in vitro, in vivo, in organoids, and in human organs. In humans, UDCA treatment also decreased ACE2 levels in the nasal epithelium, a primary site for SARS-CoV-2 infection. The retrospective study also demonstrated that patients on UDCA were less likely to develop moderate and severe COVID-19. Altogether, this study demonstrates: (1) FXR directly regulates ACE2 expression; (2) ACE2 levels closely associate with SARS-CoV-2 entry; (3) UDCA could be used as a prophylaxis or a therapy for COVID-19.[110]

Viral protein modifications are functionally essential in life cycles of coronaviruses. Targeting the post-translation modifications is promising.[111–113] The lipid modification on S protein is indispensable in SARS-CoV-2 entry. Structural analysis reveals substantial conformational rearrangements of RBD during the infection process: a switch from a closed conformation to an open conformation. In a closed conformation, RBD is buried and less accessible for ACE2 binding; while in an open conformation, RBD exposes the receptor binding motif, enabling ACE2 binding.[114–117] A hydrophobic pocket in S protein was detected, into which linoleic acid fits well. Although the linoleic acid binding pocket is distal from the receptor binding motif, linoleic acid binding results in stabilization of the closed conformation of S protein and compaction of homotrimer architecture, consequently reducing ACE2 binding and membrane fusion.[118] Another computational simulation also showed that the presence of linoleic acid in

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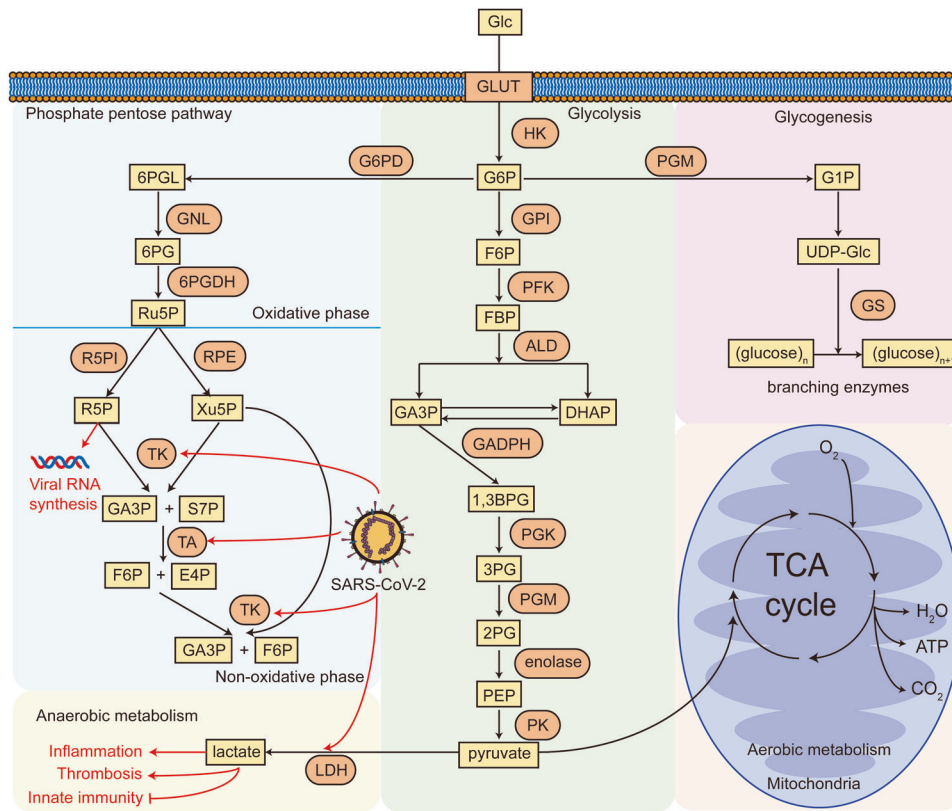Chen et al.

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Fig. 3 Major pathways of glucose metabolism. Glycolysis, glycogenesis, phosphate pentose pathway, aerobic metabolism, and anaerobic metabolism are included. GLUT glucose transporter, Glc glucose, G6P glucose-6-phosphate, F6P fructose-6-phosphate, FBP fructose-1,6-biphosphate, GA3P glyceraldehyde-3-phosphate, DHAP dihydroxyacetone phosphate, 1,3BPG 1,3-biphosphoglycerate, 3PG 3-phosphoglycerate, 2PG 2-phosphoglycerate, PEP phosphoenolpyruvate, G1P glucose-1-phosphate, UDP-Glc uracil-diphosphate glucose, 6PGL 6-Phosphogluconolactone, 6PG 6-phosphogluconate, Ru5P ribulose-5-phosphate, R5P ribose-5-phosphate, Xu5P xylulose-5-phosphate, S7P Sedoheptulose-7-Phosphate, E4P erythrose-4-phosphate, HK hexokinase, GPI glucose-6-phosphate isomerase, PFK phosphofructokinase, ALD aldolase, GADPH glyceraldehyde-3-phosphate dehydrogenase, PGK phosphoglycerate kinase, PGM Phosphoglycerate mutase, PK pyruvate kinase, GS glycogen synthase, G6PD glucose-6-phosphate dehydrogenase, GNL gluconolactonase, 6PGDH 6-phosphogluconate dehydrogenase, R5PI ribose-5-phosphate isomerase, RPE ribulose-5-phosphate 3-epimerase, TK transketolase, TA transaldolase, LDH lactate dehydrogenase

S protein stabilizes the closed conformation and blocks its interaction with ACE2.[119] Molecular dynamics simulation revealed that the linoleic acid binding site is coupled to functionally relevant regions of S protein. Removal of a ligand from the linoleic acid binding site disturbed the dynamics of distant functionally important regions of S protein.[120]

Several studies have reported that protein *palmitoylation* is crucial in host-virus interaction.[121–123] Viral protein palmitoylation has a selective advantage among coronaviruses, and the palmitoylation sites are conservative.[122] SARS-CoV-2 S protein contains a highly conserved free fatty acid binding pocket with unknown evolutionary selection advantage.[124] Quite contrary to linoleic acid, S protein palmitoylation functionally promotes SARS-CoV-2 entry. Palmitoylation site C15 at the N terminus and other sites locating in the cytoplasmic tail of S protein have been identified by two independent studies.[125,126] Zinc finger DHHC domain-containing palmitoyltransferase (ZDHHC) inhibitor reduces S protein palmitoylation, consequently decreasing S-mediated syncytia formation and SARS-CoV-2 pseudovirus entry.[125] Mutation of palmitoylation sites in the cytoplasmic tail culminated in impeded SARS-CoV-2 pseudovirus entry. The inhibitory effect could be attributed to reduced S protein homotrimer stabilization by depalmitoylation.[126] ZDHHC5 and GOLGA7 together form an acyl-transferase complex that mediates protein palmitoylation. The interaction between SARS-CoV-2 S protein and ZDHH5/GOLGA7 complex has been confirmed for

S protein palmitoylation.[127] Another study suggested that S-acyltransferase ZDHHC20 and 9 mediate the palmitoylation of SARS-CoV-2 S protein.[128] Palmitoylation sites have also been observed in the cysteine-rich domain of SARS-CoV S protein, indicating the conservation of S protein palmitoylation.[129,130]

High glucose levels promote SARS-CoV-2 entry by upregulating ACE2 expression. The major glucose metabolism pathways are shown in Fig. 3. In vitro assay demonstrated that high glucose levels significantly stimulated ACE2 overexpression in A549 cells.[131] The correlation between elevated ACE2 expression and diabetes mellitus was also confirmed in mice models.[132] A phenome-wide Mendelian randomization study revealed a significant correlation between elevated ACE2 expression and T2D.[133] Furthermore, diabetes patients are often treated with ACE inhibitors and hypoglycemic drugs that can upregulate ACE2 expression.[134–137] Notably, elevated ACE2 expression has been directly linked to reinforced viral entry. Increased ACE2 expression in lungs, kidneys, myocardium, and pancreas can promote SARS-CoV-2 binding.[138,139] A recent study indicated that glucose treatment induced a dramatic upregulation of ACE2 expression in human kidney organoids, consequently promoting SARS-CoV-2 infection. More importantly, kidney cells from the biopsies of diabetic patients were more susceptible to SARS-CoV-2 infection compared to the kidney cells from healthy controls. From a mechanistic view, hyperglycemia increases the stability of ACE2 mRNA, partially explaining the ACE2 overexpression.[140] Therefore,

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preexisting diabetes, hyperglycemia, and associated medications predispose patients to severe COVID-19 partially via promoting viral entry by upregulating ACE2 expression.

Viral protein glycosylation plays critical roles in mediating protein folding, stabilization, interaction with host factors, and immune evasion.[111,141] Beside lipid modifications, S protein of coronaviruses is also highly glycosylated.[142–144] Twenty-two N-linked glycosylation sites and several O-linked glycosylation sites have been identified in SARS-CoV-2 S protein and confirmed by mass spectrometry. The glycan types of the O- and N-linked glycosylation have also been investigated.[145–149] A high through-put study revealed that mutations at the glycosylation sites could significantly affect the infectivity of S protein pseudo-viruses. The mutations in glycosylation sites at RBD impaired viral infectivity by over 100-fold, suggestive of their functional significance. Furthermore, mutations in glycosylation residues affected the viral sensitivity to antibodies. N165Q mutation increased the sensitivity to neutralizing monoclonal antibodies, while N234Q mutation attenuated it.[150] The importance of N-glycans at N165 and N234 in modulating conformational dynamics of S protein was also highlighted by a computational simulation.[151] STT3A is a crucial glycosyltransferase that catalyzes N-glycosylation of S protein. N-linked glycosylation inhibitor 1 (NGI-1) inhibits STT3A to reduce S protein N-glycosylation. NGI-1 treatment dramatically decreased the binding ability of recombinant S protein to ACE2 and impaired the infectivity of SARS-CoV-2.[152] Blockade of S protein N-glycosylation by genetic approaches or kifunensine (mannosidase-I alkaloid inhibitor) only had a mild impact on S protein-ACE2 binding, but markedly reduced pseudo-virus entry. It is well known that S1-S2 site cleavage is closely associated with viral entry.[153,154] Interestingly, the inhibitory effect on reduced N-glycans is mediated through an enhanced S1-S2 site cleavage.[155] O-glycans of S protein were also demonstrated to modulate S1-S2 site cleavage. UDP-Gal-NAc:polypeptide N-acetylgalactosaminyltransferases 1 (GALNT1) catalyzes O-glycosylation in residues proximal to the S1-S2 site. O-glycosylation near the cleavage site significantly impeded furin cleavage and syncytia formation. The O-glycosylation is dependent on P681. P681 mutation significantly decreased furin cleavage, O-glycosylation, and syncytia formation.[156] In conclusion, both N- and O-glycosylation of S protein affect SARS-CoV-2 entry, partially via disturbing furin cleavage at the S1-S2 site. Targeting enzymes required for S protein glycosylation by inhibitors, such as 2-deoxy-d-glucose (2-DG) or NGI-1, are promising to be used for COVID-19 therapy.[157]

Virus replication

SARS-CoV-2 reorganizes the ER network and alters the morphology of this organelle to generate viral replication compartments, which contain predominantly DMVs, but also incorporate ER connectors, double membrane spherules, and multi-membrane vesicles. Results from electron tomography showed that DMVs of SARS-CoV-2 are tethered to ER, and several DMVs are attached to the same ER branch, implicating the derivation of DMVs from ER.[22] Several independent studies indicated that SARS-CoV-2 can usurp certain stages of the autophagy pathway for DMV formation. Class III phosphatidylinositol 3-kinase (PI3K) mediates autophagosome formation in the autophagy pathway. SARS-CoV-2 uses PI3K to produce phosphatidylinositol 3-phosphate (PI3P) for DMV formation, and PI3K inhibition or genetic depletion profoundly impaired DMV formation and viral replication.[158] Several SARS-CoV-2 viral proteins are proposed to manipulate the autophagy pathway. ORF7a reduces lysosome acidity to prevent autophagosome degradation. ORF3a blocks the fusion between lysosomes and autophagosomes, consequently causing the retention of autophagosomes.[159,160] The degradation of autophagy-initiating protein Beclin-1 (BECN-1) induces the fusion of autophagosomes with lysosomes, and this process is regulated by Akt/SKP2 pathway.[161]

In lung samples of COVID-19 patients, phagophore-incorporated autophagy markers LC3B-II and p62 were detected, indicating autophagosome accumulation, which can be attributed to the impact of SARS-CoV-2 on BECN1 levels through AKT1/SKP2 signaling.[162] Research on other coronaviruses also underlines the importance of the autophagy pathway in viral DMV formation.[163,164] In DMVs, viral RNA and NSPs assemble into RTCs and trigger RNA synthesis.[165]

Diverse metabolism processes, including fatty acid oxidation, cholesterol catabolism, pentose phosphate pathway, one carbon metabolism, and fatty acid synthesis, are manipulated to fulfill high substrate and energy demand for the replication of (+) ssRNA viruses.[30,166–168]

Phosphatidic acid (PA) is generated by acylglycerolphosphate acyltransferase 1 and 2 (AGPAT1/2) in the ER. It was postulated that PA subverts ER membrane to form replication organelles of SARS-CoV.[169] During SARS-CoV-2 infection, AGPAT1/2 were recruited to RTCs and critically contribute to SARS-CoV-2 replication and DMV formation. Pharmacological inhibition of PA synthesis impaired autophagosome-like DMV formation.[170] Phosphatidic acid phosphatase 1 (PAP1) converts PA to diacylglycerol, a substrate for phosphatidylethanolamine (PE) and phosphatidylcholine (PC) synthesis.[171] Intriguingly, inhibition of PAP1 activity suppressed SARS-CoV-2 replication. PE and PC are essential for (+) ssRNA viral replication via driving replication organelle formation.[172–176] Thus, inhibition of PAP1 or AGPATs likely curbs SARS-CoV-2 replication via reducing cellular downstream PE and PC levels.

Fatty acids are also essential for SARS-CoV-2 replication. Pharmacological inhibition of fatty acid synthase impaired SARS-CoV-2 replication, which was restored by exogenously supplied fatty acids.[177,178] The exploitation of fatty acids was also seen in Dengue virus infection. NSP3 of Dengue virus recruits fatty acid synthase (FASN) to the replication site and profoundly activates FASN. The author suggests that DENV could co-opt host FASN to establish its replication complexes.[179] However, available studies on the exact role of fatty acids in SARS-CoV-2 replication are lacking.

Lipid droplets play a crucial role in viral replication of different viruses including coronaviruses. Disrupting lipid droplets could be a promising therapeutic strategy.[35,180,181] Lipid droplets were considered mere lipid storages for a long time, but current findings expand their functions also as central hubs for lipid homeostasis regulation and as effectors in viral infection.[168,182,183] Lipid droplets are mainly composed of triacylglycerols, cholesteryl esters, and various enzymes for lipid metabolism, surrounded by a phospholipid monolayer.[184,185] Lipid droplet generation is regulated by several enzymes. FASN yields fatty acids, which are further converted to diacylglycerols, and then to triacylglycerols by diacylglycerol o-acyltransferase 1 and 2 (DGAT1/2). Key enzymes responsible for cholesterol synthesis in lipid droplets are acyl-CoA cholesterol acyltransferase 1 and 2 (ACAT1/2).[186,187] Since lipid droplets are involved in the replication of many RNA viruses, it is postulated that they probably affect SARS-CoV-2.[188] Lipid droplets are found to be located in close proximity to intracellular SARS-CoV-2 particles. In addition, A 922500, a DGAT-1 inhibitor, decreased viral load and ameliorated cytopathy.[189] DGAT1/2 and lipid droplet stabilizer adipocyte differentiation-related protein (ADRP) can assist SARS-CoV-2 replication. SARS-CoV-2 N protein is demonstrated to upregulate DGAT1/2 expression to generate lipid droplets. N protein interacts with ADRP on the lipid droplet surface to favor viral replication.[190] Peroxisome proliferator-activated receptor-α (PPAR-α) induces lipid droplet degradation by β-oxidation. Palmitoylethanolamide (PEA), a PPAR-α agonist, significantly suppressed SARS-CoV-2 replication by decomposing lipid droplets.[191] NSP6 was proposed to mediate the contact of SARS-CoV-2 replication organelle with lipid droplets by recruiting the lipid droplet-tethering complex DFCP-1.[192]

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TMEM41B, an ER-localized protein, has been identified as a mediator for lipid mobilization from lipid droplets.[193,194] TMEM41B is a paramount host factor with diverse functions in coronavirus replication.[195,196] Two independent genome-wide screens identified TMEM41B as an important host factor for SARS-CoV-2 replication. Inhibition or genetic ablation of TMEM41B attenuated SARS-CoV-2 replication in an early post-entry stage. Although TMEM41B is involved in the autophagy pathway,[197,198] the impact of TMEM41B on lipid localization and trafficking from lipid droplets mainly accounts for assisting viral replication since knockout of TMEM41B did not compromise SARS-CoV-2 replication via suppressing the induction of autophagosomes.[199,200] Collectively, the above studies suggest that TMEM41B mediates the lipid exchange between SARS-CoV-2 replication organelle and lipid droplets. In a genome-wide CRISPR/Cas-9 knockout screen, TME41B was also identified as a conserved host factor required for replication among coronaviruses.[201]

It is well-known that SARS-CoV-2 infection also causes a shift of **glucose metabolism** to aerobic glycolysis, namely the Warburg effect.[202–204] Most viruses including coronaviruses induce Warburg effect in favor of their replication.[205] Glycolysis provides energy and building blocks for nucleotide synthesis, which is conducive to viral RNA replication. Other viruses are reported to hijack glycolysis for RNA and protein synthesis.[205,206] Metabolomic analysis showed lower intracellular glucose levels and higher lactate levels at early time points after SARS-CoV-2 infection, suggestive of enhanced glycolysis to meet the massive demand for viral replication.[207] Proteomics study revealed an increased protein cluster of carbon metabolism during SARS-CoV-2 infection, and blockade of glycolysis by 2-DG prevents SARS-CoV-2 replication.[208] It was also reported that SARS-CoV-2 triggered ROS production to stabilize HIF-1α, culminating in the Warburg effect.[209] Moreover, the blockade of HIF-1α by GW6471 effectively inhibited SARS-CoV-2 infection in airway organoids.[210]

The **Warburg effect** leads to an increase in the activity of hexokinase (HK), which is the first rate-limiting enzyme of glycolysis. HK catalyzes the generation of glucose-6-phosphate, the primary material for the pentose phosphate pathway (PPP). The PPP generates NADPH and ribose-5-phosphate to provide material and energy for a variety of cellular events.[211,212] Glucose-6-phosphate dehydrogenase (G6PD) is an important enzyme in PPP that converts glucose-6-phosphate to 6-phosphogluconolactone. G6PD was found to be upregulated in lungs obtained from deceased COVID-19 patients.[213] The PPP was also proposed to be involved in SARS-CoV-2 replication to meet the high demand for ribose-5-phosphate for viral RNA synthesis. SARS-CoV-2 infection upregulated the levels of two constituents in the non-oxidative PPP branch: transketolase and transaldolase 1. Benfooxythiamine, a transketolase inhibitor, significantly curbed SARS-CoV-2 replication. 2-DG interferes with glycolysis to reduce the material for the PPP. The combination of 2-DG and benfooxythiamine synergistically restrained SARS-CoV-2 replication, indicating that PPP inhibition and glycolysis inhibition can independently restrain SARS-CoV-2 replication.[214]

Folate is required for one-carbon unit transfer, which is essential for purine de novo synthesis. The one-carbon metabolism is shown in Fig. 4. Folate species convey one carbon unit to mediate de novo purine synthesis.[215,216] Metabolomic analysis detected the accumulation of intermediates of de novo purine synthesis in SARS-CoV-2-infected cells. Intracellular glucose and folate were found to be depleted during the infection of SARS-CoV-2, indicative of the consumption of them. Methotrexate is a folate analog that disrupts one carbon pathway. Treatment of methotrexate markedly reduced SARS-CoV-2 RNA levels, viral protein expression, and virion production, highlighting the importance of one carbon pathway and de novo purine synthesis in SARS-CoV-2 replication.[207] Notably, methotrexate is FDA-approved for inflammatory disorders with a good safety profile.
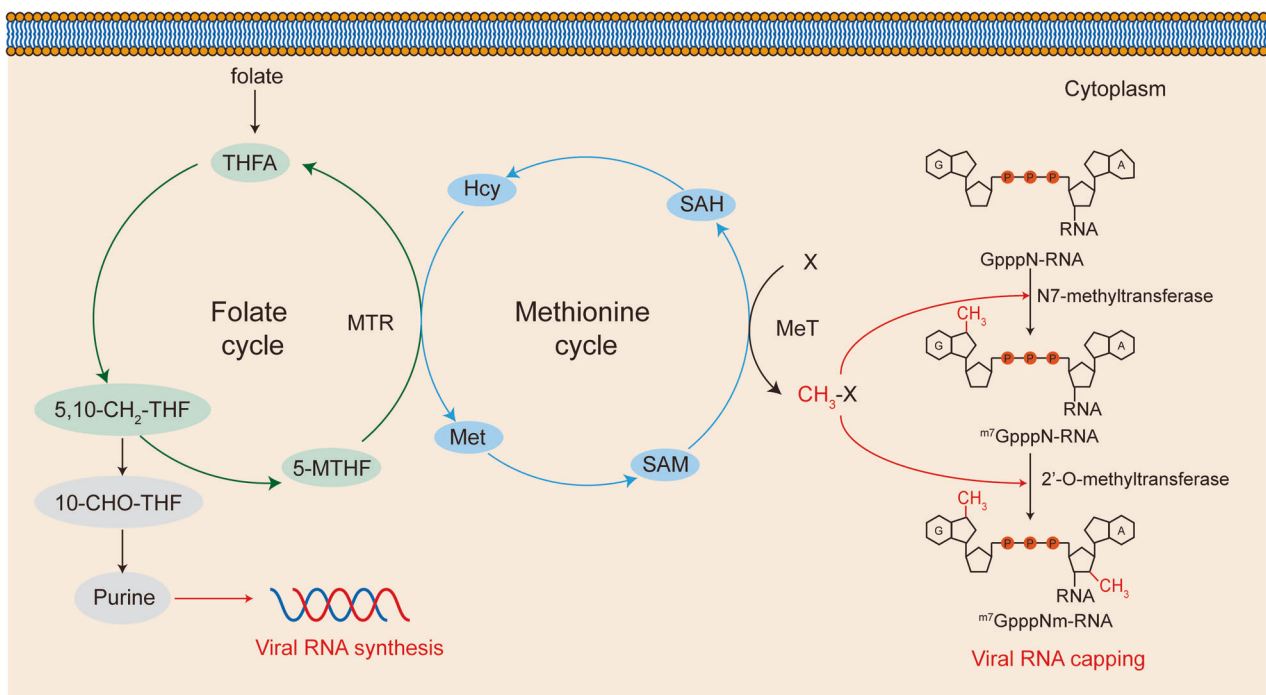

Fig. 4 One carbon metabolism. One carbon metabolism mainly contains the folate cycle and the methionine cycle. SAM provides methyl for methylation, then it is recycled by the methionine cycle. Folate drives the folate cycle to mediate transfer of one carbon unit and purine de novo synthesis. THFA tetrahydrofolate, 5-MTHF 5-methyltetrahydrofolate, 10-CHO-THF 10-formyltetrahydrofolate, 5,10-CH2-THF 5,10-methylene tetrahydrofolate, Hcy homocysteine, Met methionine, SAH S-adenosylhomocystein, SAM S-adenosylmethionine, MeT methyltransferase, MTR methionine synthase

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Thus, methotrexate is prospective to be applied to SARS-CoV-2 therapy.

One carbon metabolism also affects SARS-CoV-2 replication by boosting S-adenosylmethionine (SAM)-dependent methylation. RNA capping plays a key role in viral replication by evading the immune system, maintaining RNA stability, and initiating translation.[217] RNA capping machinery is employed by different species of coronaviruses.[218–220] SARS-CoV-2 also employs RNA capping. In SARS-CoV-2, the RNA cap is composed of a 7-methylguanosine linked to the 5′ nucleotide of the viral RNA through a triphosphate bridge. The cap is methylated at the N7 site of the guanosine, using SAM as a methyl donor, forming ^{m7}GpppN-RNA, mediated by NSP14.[221] Then, SAM-dependent 2′-O-methyltransferase adds a methyl group to the ribose 2′-O site of the nucleotide to consequently form the cap (^{m7}GpppNm-RNA), mediated by NSP16.[222] Folate metabolism fuels SAM production by maintaining the methionine cycle. The methionine cycle is essential for the generation of SAM through the adenylation of methionine.[223] SAM cycle inhibitors or genetic ablation of main enzymes in the SAM cycle were shown to dramatically restrict SARS-CoV-2 replication. More importantly, 3-deazaneplanocin A, an FDA-approved drug that can disrupt SAM production, exhibited excellent antiviral potency.[224]

Virion assembly

SARS-CoV-2 assembly occurs in the ERGIC.[27,29] Structural proteins are essential for this process. After replication, newly synthesized RNA exits DMVs through molecular phores.[25] A protein inside DMVs, probably an RNA-dependent RNA polymerase (RdRp), is hypothesized to guide the viral RNA through these pores. Viral RNA is subsequently condensed by N protein.[225] The N-RNA complex is organized to form G-shape ribonucleoproteins (RNPs). During assembly, N protein induces N-RNA complex phase separation via its central disordered domain.[225] SARS-CoV M protein interacts with N protein via their highly hydrophilic and charged carboxy groups, overlaying the N-RNA complex into the particle.[226,227] Despite functional studies on SARS-CoV-2 M protein are still blank, considering the high homology between SARS-CoV M protein and SARS-CoV-2 M protein, SARS-CoV-2 M protein possibly incorporates N-RNA complex with the same strategy.[228] The interaction between E and M in coronaviruses is well-established. Co-expression of the M and E proteins is sufficient for virion maturation and release.[229–231] E and M interacts with each other via the C-terminal domain of both proteins at the cytoplasmic side of ERGIC.[105,232] E protein is able to oligomerize to form a pentamer and serves as a cation channel to increase pH in ERGIC.[233] S is considered less involved in the assembly process since viral assembly without S is not affected.[229] S protein clusters through M-S interaction when the N-RNA complex is incorporated into a newly formed particle.[29] M is indispensable for S incorporation into virions.[227] Both M and E induce maturation and S location in ERGIC.[234]

The process of viral release is one of the least understood stages in the life cycle of SARS-CoV-2. Previously, it was a mainstream theory that coronaviruses primarily egress through the biosynthetic secretory pathway. However, a recent finding from transmission electron microscopy proposes that coronavirus including SARS-CoV-2 more likely egresses in small secretory vesicles.[235] Another study proposes a model in which coronaviruses egress by lysosomes instead of the biosynthetic secretory pathway. The lysosomes were deacidified with proteolytic enzymes inactivated in cells infected by SARS-CoV-2.[28] The mechanism of SARS-CoV-2 release remains a question of debate. Hence, there are few available studies connecting viral exit and host lipids.

Cellular lipids play crucial roles in multiple processes of SARS-CoV-2 assembly. M binds with lipid headgroups through their C-terminus domain. When M homodimer is in an open conformation, cholesterol and inositol lipids accumulate in the vicinity of the homodimer, while phosphatidylserines accumulate near a monomer of the homodimer. The author suggests that the lipid-protein interplay explains membrane curvature formation induced by M protein.[236]

E protein is a functional membrane morphogen. When synthesized alone, E reconfigures intracellular membranous organelles into elongated swirls.[237] Palmitoylation of coronavirus E protein is functionally important in viral assembly.[238–240] Palmitoylation of E protein occurs in a conserved cysteine-rich region near the transmembrane domain, which is primarily catalyzed by the DHHC-rich domain palmitoyl acyltransferase that resides in ER and Golgi. These integral membrane proteins transfer palmitate residing in the DHHC motif to the cysteine residues in the acceptor proteins.[241,242] Mouse hepatitis coronavirus (MHC) E protein has three conserved cysteine residues in their cysteine-rich regions. Replacement of cysteine residues in MHC E protein by alanines or glycines culminated in failed virus-like particle secretion and disturbed virion assembly when expressed along with N, M, and S protein.[240] Triple cysteine/alanine mutations in the cysteine-rich region led to significantly reduced MHC virus yields in the infected cells. Furthermore, MHC E protein lacking all three cysteines exhibited an increased rate of degradation, indicating a compromised stability.[243] In SARS-CoV, E also undergoes intracellular post-translational modifications. Palmitoylation of SARS-CoV E protein is functionally essential for maintaining stability.[244] Since the sequence of SARS-CoV-2 E protein is 95 % identical to the counterpart of SARS-CoV, SARS-CoV-2 E protein palmitoylation probably has a similar function. Molecular dynamic simulations on SARS-CoV-2 E protein indicate that palmitoylated E protein is more stable. In the absence of palmitoylation, the pentameric structure of E proteins lost dynamic equilibrium, and the pore radius of E protein drastically decreased and even collapsed.[245,246] Since both S and E proteins require palmitoylation to maintain their functional architecture, inhibitors targeting palmitoyl acyltransferase are of interest.

Pathogenesis

Common symptoms of COVID-19 are mild, including fever, diarrhea, and cough, accounting for ~70% of patients.[247] However, some patients progressed to more severe syndromes. Manifestations of severe COVID-19 patients are predominantly ARDS, thrombotic complications that mimic disseminated intravascular coagulopathy, and multi-organ failure. The pathology of COVID-19 is complicated and not fully elucidated, involving disruption of immune balance, systemic inflammation, complement hyperactivation, etc.[3,248]

An abnormal elevation of pro-inflammatory cytokines (IL-2R, IL-6, IL-8, TNF-α, et al.) and chemokines (CCL2, CCL8, CXCL9, et al.), together with an altered lymphocyte subset profile was observed in COVID-19 patients, reflecting the onset of autoimmune-related disorders.[249,250] Intracellular innate immunity is also disrupted by SARS-CoV-2 for immune evasion.[251] Interferon I-III (IFN I-III), nuclear factor-κB (NF-κB), toll-like receptor 4 (TLR4), retinoic-acid inducible gene I (RIG-1)-like receptor (RLR)/mitochondria anti-virus signaling protein (MAVS) pathways are all reported to be disturbed by SARS-CoV-2 with concomitant dysfunctional antiviral immunity and abnormal cytokine secretion.[252–259] In extreme cases, the immune system over-reacts to the virus and triggers a fatal cytokine storm which is characterized by uncontrolled excessive pro-inflammatory cytokine release and hyperactivated immune cells. In a cytokine storm, immune cells erroneously attack normal host cells, causing collateral multi-tissue damages and multi-organ failure, bringing poor prognosis and even mortality.[260–262] A cytokine storm was suggested as a major cause of lung damage in COVID-19.[263–265] Coagulopathy in COVID-19 patients was evidenced by significantly elevated levels of D-dimer (a biomarker of coagulopathy) and thrombocytopenia in

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hospitalized patients.[7] A large proportion of severe COVID-19 patients obtained a hypercoagulable state that predisposed patients to thrombosis. The Post-mortem of lung tissues revealed thrombogenesis in small arteries and capillaries of the pulmonary vasculature.[266–268] The etiology of thrombosis in COVID-19 is under investigation. Coagulopathy, complement activation, pro-inflammatory cytokine release, platelet hyperactivation, and endothelial dysfunction are emerging as potential major contributors to thrombosis.[269] Several compounds that ameliorate inflammation response have been demonstrated to alleviate symptoms of COVID-19. Dexamethasone is a corticosteroid widely used to treat a range of infections by resolving inflammation and suppressing abnormally elicited immune responses.[270] In patients who need ventilation, dexamethasone decreased the mortality rate by approximately one-third.[271] Baricitinib is a reversible JAK1/2 inhibitor that regulates inflammation and immune responses. In hospitalized COVID-19 patients, treatment with Barcitinib effectively decreased the mortality rate.[272] Given that host lipids have immunomodulatory properties, they are supposed to be involved in SARS-CoV-2-elicited disorders. This section focuses on the role of host metabolism in the pathogenesis of COVID-19.

Eicosanoids are inflammation mediators originated from the processing of arachidonic acid (AA). AA is generated by the cleavage of membrane phospholipids by phospholipase A_2 (PLA$_2$). AA can be processed by cyclooxygenases (COX) or lipoxygenases (LPX) to produce prostaglandins (PGs), thromboxanes (TXs), or leukotrienes (LTs), which all play regulatory roles in immune homeostasis (the AA metabolism pathway is shown in Fig. 5). Analysis of bronchoalveolar lavage fluid of COVID-19 patients showed elevated PGE$_2$, TXB$_2$, 12-HHTrE, and leukotriene B$_4$ (LTB$_4$) levels compared to healthy controls, and the eicosanoid levels were positively correlated with the levels of cytokines (IL-1α, IL-6, TNF-α, IL-12p70, IL-22, and IFN-α2) and chemokines (CCL2, CCL11, CXCL9, and CXCL10).[273]

In hospitalized patients, plasma *PLA$_2$* levels positively correlated with disease severity and acute multisystem inflammatory syndrome.[274] Lipidomic analysis on plasma samples of COVID-19 patients also identified PLA$_2$ as an indicator of severity. Deceased patients had higher levels of PLA$_2$ compared with survivors.[275] The correlation could be attributed to downstream products of AA metabolism.

COX-1 and COX-2 catalyze AA to prostaglandin H$_2$, which is further converted to diverse bioactive *prostaglandins (PGs)*. PGE$_2$, the most abundant PG, is an important mediator of a series of physiological processes, especially initiation and regulation of inflammation.[276] SARS-CoV-2 can stimulate COX-2 overexpression in diverse human cell lines.[277] Risk factors for severe COVID-19 courses include obesity, older ages, and a sedentary lifestyle, and all these risk factors positively correlated with patient serum PGE$_2$ levels. Clinical research revealed that in COVID-19 patients, high serum PGE$_2$ levels are associated with poor prognosis. The increased COX-2 levels were observed in living human precision-cut lung slices, implying the causal relationship between ARDS and PGE$_2$. Lymphopenia characterized by a drastic reduction of lymphocytes is generally accompanied by a poor prognosis of COVID-19 patients.[278] PGE$_2$ can suppress PAX5, a regulator of B cell proliferation and survival, thereby partially contributing to the lymphopenia.[279] A comparatively low level of PGE$_2$ enhances immunity while a high level of it compromises the immune system by killing lymphocytes.[280] Another prostaglandin PGD$_2$, synthesized by COX, also contributes to lymphopenia. PGD$_2$ production can be upregulated by SARS-CoV infection, which subsequently disturbs lymphocyte priming and maturation via DP1 and DP2 signaling.[281] The physiological function of PGE$_2$ and PGD$_2$ are double-edged and dose dependent. Both PGE$_2$ and PGD$_2$ can induce a lipid mediator class switching of eicosanoid production by neutrophils from the 5-lipoxygenase pathway to lipoxins,
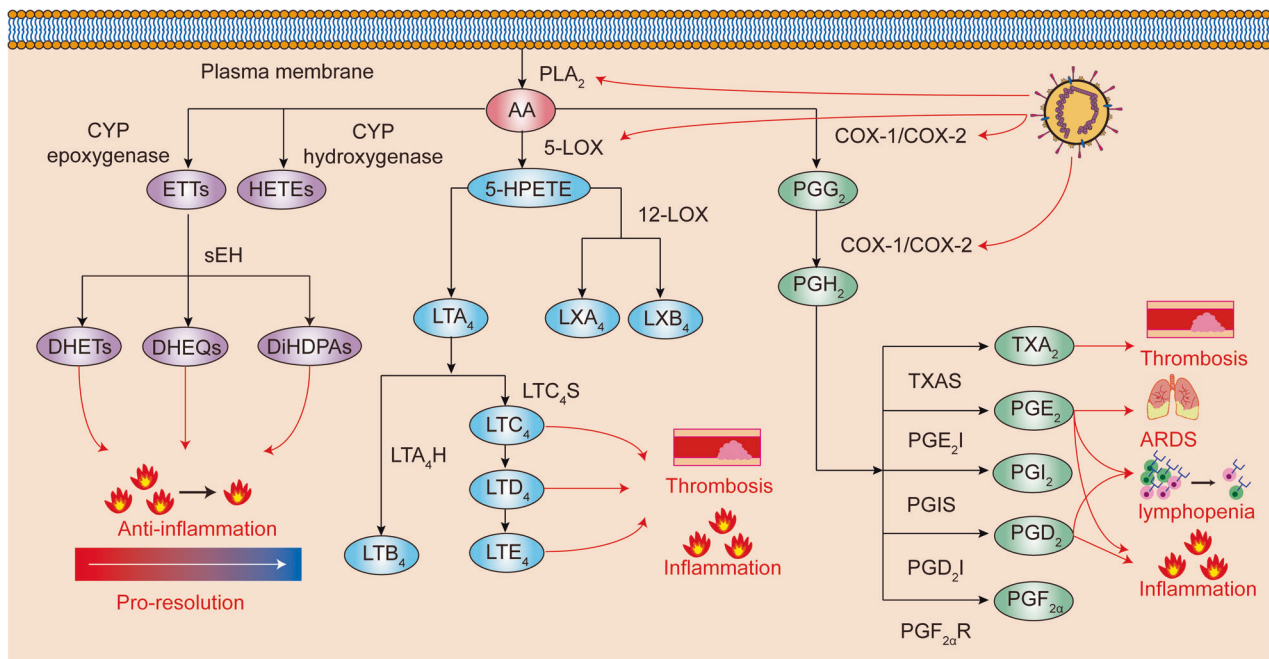

Fig. 5 Arachidonic acid metabolism. The arachidonic metabolism pathway includes three branches: 1. CYP enzymes convert arachidonic acids to ETTs or HETEs. 2. 5-lipoxygenase catalyzes arachidonic acids to lipoxins and leukotrienes 3. The COX-1/COX-2 pathway that produces prostaglandins. AA arachidonic acids, PGG2 prostaglandin G2, PGH2 prostaglandin H2, TXA2 thromboxane A2, PGE2 prostaglandin E2, PGI2 prostaglandin I2, PGD2 prostaglandin D2, PGF2α prostaglandin F2α, 5-HPETE 5-hydroperoxyeicosatetraenoic acid, LXB4 lipoxin B4, LXA4 lipoxin A4, LTA4 leukotriene A4, LTB4 leukotriene B4, LTC4 leukotriene C4, LTD4 leukotriene D4, LTE4 leukotriene E4, ETTs epoxyeicosatrienoic acids, HETEs hydroxyeicosatetraenoic acids, DiHPAs dihydroxydocosapentaenoic acids, DHEQs dihydroxyeicosatetraenoic acids, DHETs dihydroxyeicosatrienoic acids, PLA2 Phospholipase A2, COX-2 cycloxygenase-2, COX-1 cycloxygenase-1, 5-LOX 5-Lipoxygenase, 12-LOX 12-Lipoxygenase, LTC4S LTC4 synthase, LTA4H LTA4 hydrolase, TXAS Thromboxane A synthase, PEG2I PEG2 isomerase, PGIS prostaglandin I synthase, PGD2 I PGD2 isomerase, PGF2αR PGF2α reductase, CYP cytochrome P450, sEH soluble epoxide hydrolase

resolvins, and protectins.[282] Hence, COX inhibitors should be used with caution.

Another COX downstream product thromboxane A_2 (TXA$_2$) also accounts for COVID-19 pathogenesis. TXA$_2$ is synthesized from PGH$_2$ predominantly by platelet COX. TXA$_2$ induces platelet aggregation and thrombi generation. In COVID-19 patients, P-selectin, a marker of platelet activation expressed on the surface of platelet, is overexpressed. Plasma thrombopoietin levels are also upregulated, reflecting hyperactive platelet. Platelet extracted from COVID-19 patients aggregated faster and exhibited increased spreading on both fibrinogen and collagen. Otherwise, both circulating platelet-neutrophil and platelet-monocyte aggregates increased in COVID-19 patients, reflecting platelet hyperactivation and thrombogenesis. The platelet hyperactivation can be partially explained by MAPK activation and increased TXA$_2$ production.[283,284]

Leukotrienes are produced from AA by 5-lipoxygenase. Leukotriene A_4 (LTA$_4$) is generated directly from AA, then converted to LTB$_4$ in neutrophils and monocytes. Alternatively, LTA$_4$ can also be converted to leukotriene C$_4$ (LTC$_4$) by LTC$_4$ synthase. Outside the cell membrane, LTC$_4$ is catalyzed to leukotriene D$_4$ (LTD$_4$) and leukotriene E$_4$ (LTE$_4$). LTC$_4$, LTD$_4$ and LTE$_4$ are termed cysteinyl-leukotrienes.[285] Leukotrienes act as chemotactic factors for the recruitment of lymphocytes, monocytes, and macrophages to peripheral tissues and are intimately related to the pro-inflammatory function of monocytes and macrophages.[286–288] Considering the high neutrophil infiltration and high neutrophil/lymphocyte ratios in tissues of COVID-19 patients, leukotrienes are proposed to be involved.[289] Moreover, single-cell analysis of bronchoalveolar immune cells and PBMCs from COVID-19 patients shows elevated 5-lipoxygenase expression.[290,291] Leukotrienes also trigger cytokine (TNF-α, IL-1, IL-6, CCL2, etc.) release in the microenvironment to amplify inflammatory responses.[292,293] Cysteinyl-leukotrienes activate platelet by binding with cysteinyl-leukotrienes receptors on platelet, culminating in thromboxane release and consequent coagulopathy as well as lung immuno-pathology in COVID-19.[248,294,295] Besides, leukotrienes provoke atherosclerosis, plasma leakage, and ARDS, which are canonical manifestations of severe COVID-19.[288,296] Lipidomic analysis of bronchoalveolar lavage fluid extracted from COVID-19 patients who require mechanical ventilation shows significantly elevated leukotrienes levels, predominantly LTB$_4$, LTE$_4$, and eoxin E$_4$, supporting the deleterious role of leukotrienes.[297] However, there are scarce studies on the precise role of leukotrienes in COVID-19 due to the difficulty in measuring leukotriene levels since they undergo rapid physiological metabolism. Of note, inhibition of COX could lead to an imbalance of AA metabolism and provoke leukotriene production, which partially explains why NSAIDs are of little benefit to severe COVID-19 patients.

Despite the benefit of inhibiting AA metabolism, inhibition of PLA$_2$ may also downregulate pro-resolving factors which ameliorate inflammation. AA is a substrate for another enzymatic pathway, the cytochrome P450 (CYP) system. CYP system consists of two metabolic branches: ω-hydroxylases which convert AA to hydroxyeicosatetraenoic and epoxygenases which convert AA to regioisomeric epoxyeicosatrienoic acids.[298] Epoxyeicosatrienoic acids accelerate the termination of inflammation responses by mediating an array of anti-inflammatory and pro-resolving processes.[298,299] Epoxyeicosatrienoic acids mitigate the release of pro-inflammation cytokines and chemokines, including IL-6, IL-1β, and MCP-1.[300] In vivo, epoxyeicosatrienoic acids are constantly hydrated to dihydroxyeicosatrienoic acids by soluble epoxide hydrolase (sEH). Hence, inhibiting sEH can effectively upregulate epoxyeicosatrienoic acids levels. TPPU, an inhibitor of sEH, is able to block neutrophil infiltration to the lung, decrease pro-inflammatory cytokine levels in serum and bronchoalveolar lavage fluid, and ameliorate alveolar capillary leakage in an LPS-induced acute lung injury mouse model.[301] Thus, although PLA$_2$ inhibitors

theoretically ameliorate COVID-19 by reducing downstream pro-inflammatory mediators, they possibly also hinder pro-resolution and anti-inflammation processes, consequently exacerbating the condition.

Besides AA metabolism, ASM/ceramide system also mediates inflammation and thrombogenesis during SARS-CoV-2 infection. In patients with community-acquired pneumonia, serum phospho-lipid levels greatly plunged, while ceramide levels increased and ASM activity was consistently enhanced.[302] Sphingolipids are intimately associated with inflammation. In a mouse model, genetic ablation or pharmacological inhibiting ASM activity profoundly reduced pro-inflammatory cytokine production.[303] Another study evaluated ASM serum activity in a mixed intensive care unit (ICU) population. Higher serum ASM levels in non-survivors and lower ASM levels in survivors were observed, and correlated with the mortality rates in ICU patients with systemic inflammation.[275] In endothelial cells stimulated with serum from sepsis patients, plasma ASM activity and levels were profoundly enhanced, leading to endothelial stress response and cytotoxicity. However, pharmacological or genetic inhibition of ASM improved the sepsis-induced endothelial stress.[304] More importantly, ASM also works as a pathogenic mediator of ARDS.[305] Severe COVID-19 is usually accompanied by a hypercoagulable state, and tissue factors are the primary cellular initiator of coagulation.[306,307] In common conditions, tissue factors remain cryptic, and sphingo-myelin can maintain tissue factors in the encrypted state. However, hydrolysis of sphingomyelin by ASM activates tissue factors, culminating in coagulation. SARS-CoV-2 spike protein pseudovirus markedly enhanced the procoagulant ability of tissue factors, while inhibition or silencing ASM attenuated SARS-CoV-2 pseudovirus-induced tissue factor activation.[308] Given that ASM activation plays dual roles in both viral entry and pathogenesis, ASM inhibitions are supposed to alleviate COVID-19 severity.[309]

Besides viral entry, the dysregulated cholesterol metabolism also causes deterioration of COVID-19 through modulating inflamma-tory response. It is a prevalent phenomenon that patients with lower pre-infection HDL levels underwent severe COVID-19 with higher mortality rates. Cholesterol, HDL, and LDL levels are lower in patients who underwent severe COVID-19 compared to patients with non-severe COVID-19.[310–313] Cholesterol is closely associated with immunometabolism. Cholesterol accumulation in macro-phages and other immune cells promotes inflammation by amplification of Toll-like receptor (TLR) signaling, inflammasome activation, and production of monocytes and neutrophils.[314,315] Cholesterol trafficking to ER can activate NLRP3 inflammasome, a key mediator of infection-induced inflammation, consequently promoting inflammation and pro-inflammatory cytokine secretion. Treatment with statins abrogated NLRP3 inflammasome assembly and IL-1β secretion.[316,317] Cellular cholesterol levels are mainly monitored in ER membrane by liver X receptor (LXR), Sterol regulatory element binding protein-2 (SREBP2), and erythroid 2 related factor1 (NRF1).[318] When the cholesterol content in ER decreases, SREBP-2 migrates from ER to Golgi, then it is activated and translocated to the nucleus to trigger downstream transcription.[319] SREBP-2 serves as a hub to connect cholesterol levels to immune response. Mechanistically, upon detecting the decreased intracellular cholesterol level, SREBP-2 associates with NLRP3 to form a tertiary structure that translocates to Golgi to facilitate inflammasome assembly.[320] Furthermore, SREBP-2 inter-plays with NF-κB to mediate inflammation.[321,322] Evidence supports that SARS-CoV-2 manipulates SREBP-2 to stimulate cytokine storm. SREBP-2 was highly elevated in the PBMCs of COVID-19 patients, and the mRNA levels of SREBP-2 positively correlated with disease severity. In addition, SREBP-2 C-term, the cleaved form of SREBP-2, significantly increased in the serum of severe and deceased COVID-19 patients. Treating with Fatostatin A, an SREBP-2 processing inhibitor, effectively suppressed pro-inflammatory cytokine production in the PBMCs of COVID-19

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patients. Fatostatin A can also protect human umbilical vein endothelial cells (HUVEC) from LPS stimuli, indicative of the vascular protective function.[323] It is interesting to interrogate whether circulating SREBP-2 C-term directly contributes to COVID-19 progression or not. Of note, SARS-CoV-2 infection mitigates intracellular cholesterol levels. SARS-CoV-2 likely reduces the intracellular cholesterol to activate SREBP-2.

HDL is mainly responsible for the cellular efflux of cholesterol. By promoting cholesterol efflux, HDL reduces cholesterol accumulation in immune cells.[324] HDL is proposed to have anti-inflammatory, antioxidant, antiviral, anti-coagulant, and vascular protective properties, working as pathogen scavengers that potentially involves in the removal of infectious material. In addition, HDL prevents infection of various DNA and RNA viruses by neutralization.[325–327] HDL levels negatively correlated with COVID-19 severity and decreased with the deterioration of patients' conditions, indicating that high HDL levels prevent severe COVID-19. In spite of the close association between HDL and COVID-19 severity, detailed studies on the interplay between COVID-19 and HDL are scarce. The relationship between cholesterol metabolism and immunometabolism is intertwined, and the cellular cholesterol level alteration during COVID-19 is dynamic and not fully interpreted. Better comprehension will optimize the use of statins for the treatment of COVID-19.

The association between COVID-19 and dysregulated *glucose metabolism* is bidirectional. Pre-existing T2D or hyperglycemia are identified as risk factors for severe COVID-19 with high mortality rates.[328,329] On one hand, glucose metabolism facilitates SARS-CoV-2 entry and replication. On the other hand, SARS-CoV-2 infection worsens the situation of T2D or even mediates the onset of new type 2 diabetes.[204] The interplay between dysregulated glucose profiles and poor outcomes in COVID-19 patients is complicated and not fully known. However, SARS-CoV-2 can impair islet function by directly infecting pancreatic cells. Human pancreatic cells express SARS-CoV-2 entry receptors including ACE2, TMPSSR2, and neuropilin-1 (NRP-1). SARS-CoV-2 infection can restrict insulin secretion and induce β cell apoptosis in vitro.[330] SARS-CoV-2 also infects the induced pluripotent stem cell (iPSC)-derived pancreatic cultures containing endocrine and exocrine cells and provokes inflammatory responses. Of note, the autopsy of patients who died of COVID-19 confirms the SARS-CoV-2 infectivity of the pancreas.[331] Approximately 17% of severe COVID-19 patients display an increased level of amylase and lipase (two biomarkers of pancreas injury), indicative of the caused pancreatic injury.[332] It is also proposed that the usage of steroids during the treatment might contribute to the onset of hyperglycemia and diabetes.[333] Considering the risk of hyperglycemia during infection, hospital protocols should include the management of hyperglycemia in COVID-19 patients.

Preexisting hyperglycemia or diabetes mellitus also worsens the situation of COVID-19 patients by affecting immune responses. Diabetes mellitus is characterized as a chronic inflammatory status. It is well-known that diabetes mellitus affects both innate and adaptive immunity.[334] A previous clinical study shows that subjects with impaired glucose tolerance have higher levels of plasma inflammatory cytokines including IL-6, TNF-α, and IL-18 via an oxidative mechanism.[335] Higher glucose levels stimulate inflammatory cytokine secretion of periphery blood mononuclear cells (PBMCs) and impede innate immunity by inhibiting type I IFN production.[336] Another report indicates that COVID-19 patients with diabetes mellitus have higher levels of plasma inflammatory biomarkers including C-reactive protein, serum ferritin, IL-6, and a higher erythrocyte sedimentation rate.[337] A retrospective multi-center study demonstrates that COVID-19 patients with diabetes have a higher likelihood of developing lymphopenia.[50] Monocytes infected by SARS-CoV-2 produce more inflammatory cytokines, which are further augmented by higher glucose levels. Blockade of glycolysis by 2-DG significantly decreased the viral load and

inflammatory cytokine secretion. From a mechanistic view, the infection induces ROS production to stabilize HIF-1α, consequently promoting glycolysis. This metabolic alteration of monocytes directly inhibits T cell responses, partially explaining the lympho-penia.[209] Thus, hyperglycemia and diabetes mellitus likely trigger or exacerbate inflammation to culminate in poor prognosis of COVID-19 patients. The impaired innate immunity caused by high glucose levels is also conducive to SARS-CoV-2 infection.

Lactate is a byproduct of glucose metabolism and the end-product of anaerobic glycolysis. Since SARS-CoV-2 infection enhances glycolysis, the level of lactate concomitantly increases. Recently, lactate is revealed to have diverse functions in regulating T cell proliferation, immune cell metabolism, macrophage polarization, and cytokine production.[338–341] COVID-19 patients with higher lactate levels tend to worse outcomes.[342] The lactate generation is catalyzed by lactate dehydrogenase (LDH). LDH regulates the interconversion of pyruvate and lactate, which is a crucial step in the anaerobic metabolism of glucose. The high LDH levels correlate with disease progression in COVID-19 patients.[328,343,344] Besides being used as an indicator of severe COVID-19, lactate potentially contributes to disease progression. Lactate can rewire CD4+ T cell metabolism, leading to a deterioration of chronic inflammation diseases.[340] Results from a previous study show that high lactate levels are associated with more prothrombotic fibrin properties and neutrophil extracellular trap (NET) formation, which are crucial mediators of coagulopathy in COVID-19.[345,346] Moreover, lactate is an activator of HIF-1α. Lactate preconditioning can shift cellular glucose metabolism to glycolysis. By stabilizing HIF-1α, lactate promotes glycolysis in a positive feedback manner, thus facilitating SARS-CoV-2 infection.[347,348] Intriguingly, lactate is also a suppressor of RLR-mediated innate immunity. Pattern recognition receptor RLRs are RNA sensors for triggering innate immune responses against viral infection. Lactate inhibits RLR signaling and type I IFN production by preventing MAVS mitochondrial localization/aggregation, and RIG-1-MAVS association. Reduction of lactate levels by pharmacological inhibition of lactate dehydrogenases A (LDHA) profoundly increased the resistance of mice against viral infection by upregulating type I IFN production.[349] This finding explains the potential benefits of shifting glucose metabolism towards glycolysis for evading innate immune responses. However, the exact role of lactate in the pathogenesis of COVID-19 is intricate and not exhaustively studied.

Human intestines are inhabited by over 2000 species of microbes *(microbiota)*. It has been shown gut microbiota have many biological functions including shaping and modulating immune responses. Dysbiosis of gut microbiota could lead to aberrant immune responses or autoimmune diseases.[350,351] More importantly, the composition of gut microbiota is closely related to inflammatory cytokine secretion, which is surprisingly reminiscent of the inflammatory comorbidities and cytokine storm caused by COVID-19.[352] Analysis of stool samples from COVID-19 patients revealed that the composition of microbiota in COVID-19 patients underwent significant alterations. The abundance of probiotics was depleted meanwhile the abundance of opportunistic pathogens increased. The baseline abundance of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* increases with disease severity. On the other hand, the abundance of *Faecalibacterium prausnitzii* inversely correlates with COVID-19 severity.[353] Another study showed that COVID-19 patients had markedly less bacterial diversity, and the impaired bacterial diversity was associated with increased severity. This study also identified a decreased abundance of *Bifidobacterium*, *Faecalibacterium*, and *Roseburium*, and an increased abundance of *Bacteroides* in COVID-19 patients comparing to exposed controls.[354] The levels of plasma cytokines and inflammatory markers in COVID-19 patients were closely associated with microbiota composition, linking gut microbiota to COVID-19-induced inflammatory

disorders and tissue damage. Several species known to play immunoregulatory roles in human gastrointestinal tracts including *Bifidobacterium adolescentis*, *Eubacterium rectale*, and *Faecalibacterium prausnitzii* are depleted in COVID-19 patients. However, this study demonstrated no differences in bacterial diversity between COVID-19 patients and healthy controls.[355] Since the study of human microbiota is still in its cradle, how SARS-CoV-2 affects microbiota is not fully elucidated yet. COVID-19 is accompanied by a set of sequelae even after complete disease resolution, namely long COVID-19 or post-COVID-19 syndromes, including fatigue, memory loss, anxiety, anosmia, and depression.[356,357] Gut microbiota is closely related to long COVID-19. Altered microbiota composition and decreased bacterial diversity were detected in post-COVID-19 patients, even eight months after acute disease resolution.[358] Patients with long COVID-19 had distinct microbiota composition compared to completely recovered patients. While there was no significant difference in microbiota between patients with or without antibiotic treatment, indicating that the difference was not due to antibiotic use. Intriguingly, different post-COVID-19 syndromes were associated with different microbiota patterns. For example, respiratory symptoms were positively correlated with opportunistic pathogens, while neuropsychiatric symptoms and fatigue were accompanied by changes in nosocomial pathogens. More importantly, composition at admission can predict the onset of post-COVID-19 syndromes, underlining the important role of microbiota.[359] Of note, microbiota composition could be modified by dietary supplements. Some researchers suggested replenishment of probiotics by a plant-based rich fiber diet or other nutritional modulations that could be beneficial to COVID-19 patients.[360–363] Otherwise, the influence on microbiota should be taken into consideration when using antibiotics for the treatment of COVID-19 patients. Compared with gut microbiota, lung microbiota was less investigated. However, recent findings support that lung microbiota also played an important role in COVID-19 pathology. Lung microbiota is involved in respiratory infections diseases and pneumonia.[364,365] But due to the difficulty in measuring the composition of the microbial community in patients, the role of lung microbiota in COVID-19 is poorly understood.

As mentioned above, *long COVID-19* is manifested by a series of post-infection syndromes even a long period after the nucleic acid test shows a negative result. Over 200 symptoms have been identified in long COVID-19, some of them were severe and debilitating. For example, a meta-analysis showed that 22% of patients had cognitive impairment 12 weeks post-infection.[366] Cognitive impairment is a canonical symptom of long COVID-19. The magnitude of cognitive impairment in long COVID-19 is equal to 10 years of cognitive aging, and likely increases over time.[367] It is even more concerning that hospitalized and non-hospitalized patients have similar rates of developing cognitive impairment.[368] Otherwise, many patients have other sequelae including multi-organ dysfunction, gastrointestinal disorders, respiratory disturbances, and cardiovascular disorders.[369–371] The etiology of long COVID-19 is multifactorial. Major contributors to long COVID-19 are proposed to be abnormally altered immune system, circular system dysfunction, multi-organ damage, and neuroinflammation.[372,373] Considering the deleterious effect of long COVID-19, exploring the mechanism and prophylaxis is of importance. Many long COVID-19 patients shared similar symptoms with Myalgic encephalomyelitis/chronic fatigue syndromes (ME/CFS), a multi-system neuroimmune disorder that generally happens after infection. ME/CFS was manifested by chronic fatigue, cognitive impairment, and post-exertional malaise.[374,375] Therefore, therapeutic strategy for ME/CFS presumably also alleviated COVID-19. Dietary supplementation of coenzyme Q can reduce fatigue and oxidative stress in ME/CFS.[376] The effect of coenzyme Q on long COVID-19 is being clinically tested. It is also noted that mast cell activation was prevalent in long COVID-19 patients, implying the

causal link between mast cell activation and long COVID-19.[377,378] The proposed mechanism is that aberrant mast cell activation triggers mediators including histamine, cytokines, leukotrienes, and prostaglandins, bringing damage to multiple tissues. Anti-histamine treatment is the protocol for mast cell activation syndrome. Pilot studies have demonstrated that antihistamines can relieve long COVID-19-associated symptoms.[379,380] Some components of traditional herbs including quercetin and luteolin are also proposed for the prevention or treatment of long COVID-19, although there is no clinical evidence till now.[381] It is noteworthy that physical exercises exacerbate the condition of COVID-19 patients instead of improving it. According to a survey, regular physical exercises worsened the condition of 74.84% long COVID-19 patients, only 0.84% patients reported improvement by physical exercises.[382] Hence, long COVID-19 patients should take caution when practicing. Although long COVID-19 brings enormous health burdens to patients, there are few clinical studies available now.

Drug repurposing
Patients with severe COVID-19 undergoing mechanical ventilation have a poor prognosis, and even some recovered patients have severe sequelae, such as lung fibrosis, chronic vasculitis, hypertension, and embolism.[383,384] Considering the urgency, repurposing FDA-proved drugs with a verified safety profile is of interest. This section focuses on the repurposing of FDA-proved drugs that intervene in host lipid metabolism for the treatment of COVID-19 and their clinical research. The clinical trials are summarized in Table 1.

Statins. Statins have been applied in clinic for decades with a proven efficacy and safety for the treatment of hyperlipidemia and as prophylaxis of atherosclerosis disease.[385] HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase (HMGCR) is a rate-limiting enzyme for cholesterol biosynthesis. Statins are strong competitive inhibitors of HMGCR and are generally used as lipid-lowering drugs. Statins effectively reduce plasma cholesterol levels by inhibiting cholesterol biosynthesis and lowering low-density lipoprotein (LDL) levels.[386] Since cellular cholesterol plays a critical role in SARS-CoV-2 viral entry, statins have bright prospects for treating COVID-19.

Clinical reports of COVID-19 patients revealed a correlation between cholesterol metabolism and prognosis. Statistical analysis shows that a higher serum high-density lipoprotein cholesterol (HDLc) level predicts a lower mortality rate before infection by SARS-CoV-2.[310] Total cholesterol, LDL, and HDL levels decreased in COVID-19 patients compared to the levels prior to infection. Total cholesterol and LDL recovered to baseline in discharged patients but progressively dropped in non-survival patients.[387] Given that statins manage cholesterol profiles, they could improve the conditions of COVID-19 patients.

Aside from regulating cholesterol levels, statins have diverse effects independent of HMGCR inhibition, including stabilizing endothelial dysfunction, regulating atherosclerosis, anti-fibrosis, anti-thrombosis, anti-oxidantion, anti-apoptosis, and anti-inflammation.[388] The impact of statins on ARDS is controversial, two clinical studies show no improvement in ARDS under statins treatment versus placebo.[389,390] While another study indicates a potential benefit to ARDS patients associated with statin use.[391] Meta-analysis indicates that statin practically prolongs ventilator-free days of patients with ARDS, although it does not improve mortality and severe sepsis.[392]

A retrospective study of COVID-19 patients shows that the 28-day all-cause mortality rate was 5.2% and 9.4% in the matched statin and non-statin groups, respectively.[393] Another retrospective study confirms that COVID-19 patients admitted to ICU who used atorvastatin had a slower progression to death and a lower mortality rate.[394] Meta-analysis of 19 studies involving

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Table 1. Summary of metabolism-modulating drugs

Drug name	Clinical trial	Phase
Statins		
Simvastatin	NCT04348695	II
	NCT05542095	I
Rosuvastatin	NCT04472611	III
	NCT04359095	III
	NCT04472611	III
	NCT05594615	I
Atorvastatin	NCT04631536	III
	NCT04486508	III
	NCT04952350	III
	NCT04380402	II
	NCT04813471	III
	NCT04904536	III
	NCT04801940	III
	NCT04380402	II
	NCT04466241	III
ASM inhibitors		
Fluoxetine	NCT04377308	IV
	NCT05041907	II
	NCT05283954	III
	NCT04920838	III
	NCT04780152	III
Fluvoxamine	NCT04718480	II
	NCT04342663	II
	NCT04668950	III
	NCT04727424	III
	NCT05087381	IV
	NCT04510194	III
	NCT04711863	II
NSAIDs		
Aspirin	NCT05073718	III
	NCT04368377	II
	NCT04324463	III
	NCT04365309	III
	NCT04381936	III
	NCT04808895	III
	NCT04466670	II
	NCT04937088	II
	NCT04768179	III
Paracetamol	NCT04920838	III
	NCT04673214	III
	NCT04416334	III
	NCT04536051	III
Naproxen	NCT04325633	III
Montelukast		
Montelukast	NCT04718285	II
	NCT04695704	III
	NCT05094596	IV
	NCT04389411	III
Omega-3 fatty acids		
Omega-3 fatty acids	NCT04836052	III
	NCT05121766	I
	NCT04647604	II

Table 1. continued

Drug name	Clinical trial	Phase
	NCT04495816	II
	NCT04553705	III
	NCT04460651	III
	NCT04335032	III
	NCT05711810	IV
2-DG		
No available clinical trials		
Metformin		
Metformin	NCT04510194	III
Metformin glycinate	NCT04626089	II
	NCT04625985	II

over 395,000 patients indicates that prior statin use is associated with a lower risk of mortality and a reduced risk of severe COVID-19.[395] However, another study obtained a different result: prior treatment of statins improves neither severity outcome nor mortality rates. The contradictory results may be caused by the risk of exacerbating compensatory immune signals through the effect of statins on TLR and NF-κB.[396] In addition, results from clinical studies show that statin treatment upregulates ACE2 expression, thereby potentially facilitating SARS-CoV-2 attachment and entry. Hence, whether statins practically improve COVID-19 severity and prognosis or not remains a matter of debate.[397]

ASM inhibitors. Most antidepressants belong to functional inhibitors of acid sphingomyelinase (FIASMAs) and are widely applied as psychotropic medications. Antidepressants, such as fluoxetine, fluvoxamine, paroxetine, and amitriptyline, have been widely used for decades with proven safety.[398] As discussed above, evidence supports the central role of ASM/ceramide system during SARS-CoV-2 infection. FIASMAs, which practically reduce ceramide levels, are promising to serve as a therapeutic modality for COVID-19. They regulate pro-inflammatory cytokine secretion and thereby display anti-inflammatory properties. They also interact with ER chaperone the Sigma-1 receptor and ER stress sensor inositol-requiring enzyme 1α to regulate cytokine secretion and immune response.[399] Besides blocking SARS-CoV-2 viral entry, FIASMAs can also ameliorate COVID-19 via their immune modulatory property.[400,401]

The potency of FIASMAs has been validated. A multicenter study on hospitalized severe COVID-19 patients shows a reduced risk of intubation or death under FIASMA treatment (37.5% FIASMA group vs 41.4% non-FIASMA group). The correlation between taking FIASMAs and reduced likelihood of intubation or death is not specific to one particular class of FIASMAs.[402] Another cohort study on severe COVID-19 patients reveals that chronic prescription of FIASMA is associated with a lower risk of mortality. In this study, amlodipine exhibited the most prominent efficacy among FIASMAs. Patients treated with amlodipine before the infection had a lower rate of mortality (12.7%) than patients not treated with amlodipine before the infection (34.9%).[403] In a randomized double-blinded clinical trial, fluvoxamine reduced the likelihood of clinical deterioration compared to the placebo group.[404] In another randomized clinical trial, the proportion of patients observed in a COVID-19 emergency setting or transferred to a tertiary hospital due to COVID-19 was lower in the fluvoxamine group compared with the placebo group.[405] Collectively, these clinical results support FIASMAs as an effective modality for COVID-19.

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NSAIDs. Non-steroidal anti-inflammatory drugs (NSAIDs), the COX-1 and COX-2 inhibitors, are prospective as a therapy for COVID-19. NSAIDs are well-tolerated anti-inflammatory drugs that are widely used for managing acute or chronic inflammatory diseases. A retrospective study indicates that the use of NSAIDs is associated with a reduced risk of hospitalization of COVID-19 patients with chronic inflammatory diseases.[406] Another study obtained a similar conclusion: COVID-19 patients prescribed ibuprofen or naproxen had a lower risk of hospitalization.[407]

However, the application of NSAIDs on COVID-19 remains controversial. Some propose that NSAIDs usage upregulates ACE2 expression, thus promoting SARS-CoV-2 entry while other studies demonstrate that NSAIDs have no impact on ACE2 expression and will not exacerbate infection.[408–411] There are also concerns that NSAIDs could exacerbate hypercoagulation and the incidence of thrombosis due to decreased thrombomodulin caused by NSAID treatment.[412,413] Furthermore, NSAIDs may predispose patients to gastrointestinal and cardiovascular complications which are also canonical symptoms of COVID-19.[414]

Although the World Health Organization has declared that there is no evidence of an increased risk of disease deterioration, considering the potential adverse effects, NSAIDs should be used with caution on COVID-19 patients.

Montelukast. Montelukast is a cysteinyl leukotriene receptor antagonist that blocks the binding of cysteinyl leukotrienes. Montelukast was initially used for the treatment of chronic asthma with excellent safety. Montelukast can effectively suppress inflammation by inhibiting NF-κB activation and the downstream pro-inflammatory cytokines (IL-6, TNF-α, MCP-1, et al.) secretion in cultured human mononuclear cells and macrophages upon stimulation.[415,416] In addition, montelukast is also capable of inhibiting platelet activation under the stimulation of serum from COVID-19 patients by downregulating the surface expression of tissue factors and P-selectin. As a consequence, the formation of monocyte- and granulocyte-platelet aggregates are profoundly inhibited.[417]

Montelukast also affects the viral proteins of SARS-CoV-2. A computational simulation predicts that montelukast may bind S protein to disturb the RBD domain.[418] Montelukast sodium hydrate binds with the C-terminus domain of SARS-CoV-2 NSP1 protein to restore host protein synthesis, which is suppressed by NSP1.[419,420]

Hospitalized patients treated with montelukast experienced significantly fewer events of clinical deterioration compared with patients not receiving montelukast (10% vs 32%).[421] Montelukast treatment alleviated the severity of COVID-19, prevented lung respiratory failure, and reduced mortality.[422] Montelukast is currently under phase III clinical trial (NCT04389411) for the treatment of severe COVID-19.

Omega-3 fatty acids. Pro-resolving mediators, e.g., lipoxins, resolvins, protectins and maresins, stimulate key cellular events in resolution, namely cessation of neutrophil infiltration and enhanced macrophage uptake of debris, hence actively protecting tissues from hyperinflammation and expediting recovery from inflammatory damage.[423] Treatment with such pro-resolving mediators accelerates the clearance of bacteria and impedes neutrophil accumulation in the lung, thereby promoting the resolution of bacteria-induced lung injury.[275] These pro-resolving mediators are synthesized from two Omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic (DHA). Both serve as precursors in the biochemical pathways leading to Specialized pro-resolving mediators.[424] Therefore, exogenous supplementation of omega-3 fatty acids is recommended to treat COVID-19 via the pro-resolving process.[425]

Omega-3 index (O3I) reflects blood levels of EPA and DHA. It was revealed a lower O3I as a risk factor for severe COVID-19A study after comparison of O3I levels in hospitalized severe COVID-19 patients with ambulatory patients with mild infection.[426] A randomized double-blinded study was conducted to investigate the therapeutic effect of omega-3 fatty acid supplementation on severe COVID-19 patients. The result is encouraging, it showed that omega-3 fatty acid supplementation improved the levels of several parameters of respiratory and renal function in critically ill patients and increased the survival rate.[427] Omega-3 fatty acids are well-known as anti-inflammatory and pro-resolving factors and confirmed to improve the conditions of COVID-19 patients.[425,428]

2-DG. 2-DG is a synthetic analog of glucose that interferes with glycolysis. 2-DG has been used in diverse areas for decades, including antivirus, anticancer, and antiepileptic.[429–431] As mentioned above, SARS-CoV-2 induces the Warburg effect, and its infection highly depends on glycolysis. The transition of glucose metabolism to glycolysis favors SARS-CoV-2 entry, replication, and pathogenesis. Moreover, 2-DG also inhibits the PPP pathway and glycosylation of S protein. Hence, 2-DG is presumably promising to ameliorate the severity of COVID-19.[202,203]

2-DG treatment significantly reduced the viral load of cells infected by SARS-CoV-2 and ameliorated the CPE and cell death. Surprisingly, the progeny SRAS-CoV-2 generated from 2-DG-treated cells exhibited weakened infectivity.[432] However, 2-DG has potential toxicity. 2-DG can cause glucocytopenia in the nervous system, and irregularities in the cardiovascular, respiratory, and immunological systems.[433,434] In a randomized phase II clinical study, 2-DG was administered as an adjunct to stand of care (SOC). Patients treated with 90 mg/kg/day 2-DG had better outcomes. The clinical recovery and vital signs normalization were faster in the 90 mg/kg/day 2-DG group. However, in this study, 30.3% of patients reported adverse events.[435] In 2021, 2-DG was approved by the Drug Controller General of India as an adjunct therapy along with the SOC in hospitalized patients with mild to severe COVID-19. The clinical data indicates that patients treated with 2-DG + SOC underwent a quicker symptomatic relief and normalization of vital sign factors compared with SOC alone. The clinical data is accessible from the trials' registrations on the Clinical Trial Registry of India. Notably, continuous administrations of high 2-DG doses over a long time might cause toxicity to the individuals. Considering the adverse effects, 2-DG should be used with caution.

Metformin. Metformin has been used as a first-line anti-diabetic drug for decades. Recent research reveals that metformin also possesses anti-cancer, anti-aging, anti-inflammatory, and other properties.[436–439] Due to the prominent bioactivity of metformin, it is also proposed for the treatment of COVID-19.

Several observational studies have confirmed the beneficial effect of metformin on COVID-19. As mentioned above, diabetic mellitus, dysregulated glucose metabolism, and hyperglycemia are risk factors for severe COVID-19. A large-scale retrospective study including over 2,800,000 COVID-19 patients with diabetes has been conducted to evaluate the influence of different glucose-lowering drugs. Patients prescribed metformin have markedly less COVID-19-related mortality rates compared with those prescribed insulin. However, several confounding factors have not been adjusted in this study.[440] Another two small-scale retrospective studies indicate that, after adjusting confounding factors, metformin use is still associated with lower mortality rates in COVID-19 patients with diabetes.[441,442] Intriguingly, the beneficial effect of metformin is shown to be gender-dependent. Metformin treatment profoundly alleviates the severity in female COVID-19 patients, while the effect on male patients is minimal. Researchers propose that this difference is probably due to the stronger suppressive effect of metformin on TNF-α production in women than in men, suggesting that metformin alleviates COVID-19 primarily via regulating inflammatory cytokines.[443] Several clinical

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trials are currently being conducted. Those clinical studies demonstrate that metformin treatment prevented disease progression and reduced mortality rates. However, further studies are needed through randomized, double-blinded clinical trials.

From a mechanistic perspective, metformin presumably ameliorates COVID-19 via multifaceted effects. Metformin can prevent endothelial dysfunction, reduce cytokine release, improve glucose metabolism, and promote resolution of lung damage after acute inflammation. All these effects are considered to be responsible for alleviating COVID-19 severity.[444–448] Considering the distinct therapeutic effect between males and females, the anti-inflammatory effect seems to play a major role. However, the practical mechanism needs to be experimentally investigated.

SUMMARY AND PERSPECTIVE
In this review, we summarize the advances and provide comprehensive knowledge of metabolic alterations induced by SARS-CoV-2 and how they influence SARS-CoV-2 infection in aspects of entry, replication, assembly, and pathogenesis. We also include studies of drugs repurposed for COVID-19.

Like other coronaviruses, SARS-CoV-2 entry entails the intact lipid rafts on cell membranes.[449–451] The paramount importance of lipid rafts during SARS-CoV-2 entry was underpinned and summarized by several researchers.[75,452] The role of cellular cholesterol metabolism is controversial and not fully interpreted. Some researchers suggest that SARS-CoV-2 down-regulates cellular cholesterol levels, and increased cholesterol levels impede SARS-CoV-2 infection. However, others suggest that cholesterol depletion restrains SARS-CoV-2 infection. The inconsistent results could be due to different time points, positions, treatments, methods, and so forth. The exact role of cholesterol entails further studies. Cholesterol might influence SARS-CoV-2 infection in post-entry stages including replication, virion maturation, and egress, although there is currently no available study. It would be also interesting to interrogate how increased cellular cholesterol restrains SARS-CoV-2 infection. Ceramides assist SARS-CoV-2 entry by forming ceramide-rich microdomains where ACE2 clusters. Contrarily, sphingosine, the downstream metabolite of ceramides, impedes SARS-CoV-2 entry by blocking the interaction between S protein and ACE2. S1P is a product downstream of sphingosine. The anti-inflammatory and anti-thrombotic properties of S1P are well-established. S1P is postulated to ameliorate COVID-19 by protecting endothelial barrier, although there is no available study.[453,454] Considering the intimate relationship between COVID-19 and sphingomyelin metabolism, other components in sphingomyelin are probably involved in different stages of SARS-CoV-2 infection. Interrogating the ER branch of sphingomyelin metabolism would be of interest since SARS-CoV-2 replication organelles are also derived from ER. Lipid modifications of S protein have been intensively investigated. The modification by linoleic acid locks the S protein in a closed conformation and prevents viral entry, while the palmitoylation of the S protein stabilizes the S protein homotrimer, thereby promoting viral entry. S protein of MHV is also demonstrated to be palmitoylated, and mutation at the palmitoylation sites impeded MHV penetration into cells and reduced specific infectivity, indicating the conservation of S protein palmitoylation among coronaviruses.[455] Hyperglycemia or diabetes mellitus facilitates SARS-CoV-2 entry by upregulating ACE2, partially accounting for the worse situation of COVID-19 patients with preexisting diabetes. The glycosylation of S protein also significantly contributes to viral entry.

Host lipids also contribute to SARS-CoV-2 replication. The glycerophospholipid metabolism pathway facilitates SARS-CoV-2 replication by facilitating DMV formation. However, which step of the glycerophospholipid metabolism is responsible remains unknown. PE and PC are downstream metabolites of PA, and both were reported to hijack RNA virus replication,[173,175,176,456] but currently there is no available data on the role of PE and PC in SARS-CoV-2 replication. Deciphering the roles of PC and PE during SARS-CoV-2 infection is of interest. The employment of host LDs by SARS-CoV-2 to meet the energy and material demand for replication was evidenced by current findings. The involvement of LDs was well-elucidated in other RNA viruses including hepatitis C virus, rotavirus, Zika virus, and dengue virus.[181,457–460] The PPP generates nucleotides for viral replication, partially explaining the benefit of the Warburg effect induced by SARS-CoV-2. The onset of the Warburg effect is also seen in other virus infection.[205,461,462] One carbon metabolism provides material for SARS-CoV-2 RNA capping, which is important for viral replication. The cap formation is conveyed by NSPs, primarily NSP9, and NSP12.[463,464] Capping at the 5' of viral RNA can prevent RNA degradation by innate immune responses and facilitates viral protein translation.[222] Of note, phosphatidylinositol phosphate biosynthesis is revealed to be essential for SARS-CoV-2 infection. SARS-CoV-2 infection is highly dependent on phosphatidylinositol phosphate biosynthesis.[86,87] In addition to contributing to replication compartment formation, phosphatidylinositol phosphate biosynthesis likely promotes SARS-CoV-2 in different stages of its life cycle. Further studies would be of interest.

The next section depicted how host lipids assist SARS-CoV-2 assembly. M protein uses several lipid components to induce membrane curvature. E protein palmitoylation is supported by computational simulations, and the adduct of palmitate is able to maintain E protein functional architecture. It was previously hypothesized that β-coronaviruses employ the biosynthetic pathway for egress. However, recent findings suggested β-coronaviruses employ deacidified lysosomes for virion release.[28,465,466] Due to a paucity of comprehension of coronavirus egress mechanism, related studies are insufficient. Considering that the lysosomes are intimately connected to the lipid metabolism of LDs and ER, research on the association between host lipids and viral exit is warranted.[467,468]

Severe COVID-19 is manifested by ARDS, hyperinflammatory status, thrombotic complications, and multi-organ failures. This paper reviewed the impact of host lipids on COVID-19 pathogenesis. Eicosanoids of the AA pathway including prostaglandins, thromboxanes, and leukotrienes as well as the ASM/ceramide system are included as they affect thrombotic and inflammatory status during SARS-CoV-2 infection. The importance of cholesterol in COVID-19 is interpreted in this section. The bidirectional relationship between COVID-19 and dysregulated glucose metabolism was discussed. The role of lactate is also incorporated. Recent studies indicate that many COVID-19 patients underwent microbiota dysbiosis, and microbiota associates with COVID-19 severity via the gut-lung axis.[469–471] The alteration of microbiota composition and its important role in COVID-19 is exhaustively discussed. However, available studies on the mechanism underlying the onset of long COVID-19 are few. Treatments and prophylaxis for long COVID-19 needs to be further validated by clinical studies.

Ultimately, several lipid-modulating and glucose-modulating drugs repurposed for COVID-19 are overviewed. Statins, ASM inhibitors, NSAIDs, Montelukast, Omega-3 fatty acids, 2-DG, and metformin are summarized. Further long-term follow-up studies are needed to characterize the benefit of these drugs for treating COVID-19 patients. Coronaviruses have given rise to three pandemics with huge damage to our society in the last two decades. However, therapies with proven efficacy are still lacking till now. Understanding the interaction between coronaviruses and host metabolism will prompt antiviral drug development and better disease management that would apply not only to SARS-CoV-2 infection, but also potentially to other types of coronavirus infections.

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AUTHOR CONTRIBUTIONS
All authors have read and approved the final version of the submitted manuscript. M.-L.H. and P.C. conceptualized and designed the article. P.C. did literature research, wrote the manuscript, and drafted figures. M.-L.H., Y.H., B.J., and M.W. revised the manuscript.

ADDITIONAL INFORMATION
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