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Targeting Lipid Metabolism for Better Management of Coronavirus SARS-COV-2 Infections: Intervention, Antiviral Drug Development, and Challenges

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Commentary

The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), although has faded from public view, the virus itself remains highly active and continues to mutate, continuously causing infections. The population faces the risk of severe outcomes caused by virus infection (e.g., multi-organ tissue injury and acute respiratory distress syndrome (ARDS)) [1]. Furthermore, patients with chronic diseases (cardiovascular diseases, diabetes) are at risk of developing severe sequelae or even elevated mortality [2,3]. Hence, a deeper understanding of SARS-CoV-2 is still of interest. The review paper entitled "Metabolic alterations upon SARS-CoV-2 infection and potential therapeutic targets against coronavirus infection" provides substantial insights on how SARS-CoV-2 triggers significant metabolic alterations in its host and the intricate interplay between SARS-CoV-2 and host metabolism, indicating potential metabolic targets for therapeutic interventions. In this commentary, we compile all pathways introduced in the article and elucidate how the concept of incorporating metabolism-modulating drugs in this context serves as promising strategy for effective treatments against coronavirus disease (COVID-19), and a pivotal need in the current global health scenario.

The complex metabolic alterations and their respective constituents upon SARS-CoV-2 virus infection are based on the stages of virus replication cycle: entry, replication, assembly, and pathogenesis. The alterations highlighted are lipid metabolism, glucose metabolism, one-carbon metabolism, and amino acid metabolism, respectively [4].

Lipids metabolism is known to play prominent roles in energy supply, cellular integrity, cellular function, inflammation, and immune response. Significantly, lipid metabolism is one of the pathways closely associated with SARS-CoV-2 infection [5]. The commented article elucidated interactions between specific lipids and viral components, revealing how lipids actively participate in the viral infection process. SARS-CoV-2 entry begins with binding of viral Spike protein to angiotensin converting enzyme-2 (ACE-2) receptors on host cell membrane. While this interaction is well-documented, it is crucial to underscore the indispensable role of lipid components that facilitate the binding and lipid modifications of viral proteins in this process, as they both contribute to the effective invasion strategy.

During the process, the virus utilizes membrane lipid components to stabilize the anchorage and aid the entry into host cells:

1. Lipid rafts in cell membrane, consisting of cholesterol, provide platform for receptors including ACE2 that facilitates SARS-CoV-2 attachment and penetration [6,7];

2. Spike protein can directly interact with lipid components in cell membrane, including cholesterol [8], sphingolipids (e.g., ceramides) [9] and glycolipids (e.g., monosialylated gangliosides) [10].

The Spike protein has a trimeric structure, and actively adopts various lipid modifications that are crucial for its functionality [11]. There is structural analysis that elucidates the receptor-binding domain (RBD) of Spike undergoes conformational

changes from a closed form to open form during infection. The closed form of RBD is stabilized by linoleic acid, a polyunsaturated fatty acid. Despite the distance between RBD and linoleic acid binding site, the closed conformation of Spike is stabilized and the RBD is buried to reduce the accessibility of ACE2R [12]. While the mechanism seems counterintuitive for viral infection, there is a hypothesis that SARS-CoV-2 employs this strategy to evade host immunity [13], and preserve the viral infectivity potential by preventing the Spike switches to open conformation prior to meeting host cells expressing ACE2R. When the virus encounters the ACE2 receptor on the host cell, the binding interaction induces allosteric changes that shift the Spike protein from a closed to an open conformation, overcoming the stabilizing effect of linoleic acid and enabling viral entry [13,14].

Palmitoylation, another post-translational modification that stabilizes Spike protein via facilitating the conformational changes necessary for ACE2 binding: Palmitoylation is catalyzed by enzymes such as zinc finger DHHC domain-containing palmitoyltransferase (ZDHHC), adding a saturated fatty acid palmitic acid to specific cysteine residues on the Spike [15]. This modification stabilizes the Spike homotrimer by adding hydrophobicity, which enhances its association with the viral envelope. Consequently, palmitoylation raises the functional-structural stability, promoting viral entry and infectivity [16].

Beyond entry, cholesterol and lipid metabolism alterations are implicated in the pathogenesis of SARS-CoV-2 [17]. Cholesterol accumulation in immune cells can potently amplify inflammatory response by activating NLR family pyrin domain containing 3 (NLRP3) inflammasome and toll-like receptor (TLR) signaling, potentially contributing to inflammatory disorders or fatal cytokine storm [18]. The multifaceted role of cholesterol metabolism in COVID-19 makes statin, cholesterol-lowering drugs a potential COVID-19 treatment strategies [19]. Statins enhances endothelial functions by several mechanisms, for instance, increasing the production of Nitric Oxide, a vasodilator that exhibits anti-inflammatory property and anti-thrombotic property theoretically benefit COVID-19 patients. However the therapeutic outcomes of statins were inconsistent, which leave needs for further investigations [20].

In addition to statins, the article introduced other FDA-approved drugs targeting lipid metabolism may hold promise in treating COVID-19: Acid sphingomyelinase (ASM) inhibitors are found to hinder SARS-CoV-2 entry by reducing ceramide levels, one of the lipid components in cell membrane which facilitates the viral entry [9]. However, such findings are experiment-based, lacking theoretical explanations. Such drugs encompass antidepressants, like amitriptyline and sertraline; nonsteroidal anti-inflammatory drugs (NSAIDs) help reduce inflammation associated with SARS-CoV-2 infection by inhibiting cyclooxygenases, a kind of enzyme catalyzes the conversion of a fatty acid, arachidonic acid, and consequently inhibit downstream lipid-mediated signaling pathways that initiate inflammation. However, the conflict that whether NSAIDs upregulate the expression of ACE2R hampers the clinical application of these drugs at this moment and raises the need for further researches [21]; Omega-3 fatty acids are lipids that functions are relevant to the target of NSAIDs- arachidonic acid. Omega-3 fatty acids can replace cell membrane-arachidonic acid and compete for same enzymes, and most importantly, the downstream products are less pathogenic, eliciting anti-inflammatory effects [22] and relieving conditions among COVID-19 patients, both respiratory and renal functions are improved upon such fatty acid supplementation [23].

Despite these promising therapeutic strategies targeting lipid components and relevant pathways for viral entry and pathogenesis, it is also critical to understand how SARS-CoV-2 exploits host lipid pathways for its replication and survival. SARS-CoV-2 exploits host lipids from membrane-bounded organelles like endoplasmic reticulum (ER) to form double-membrane vesicles (DMVs), enacting protective functions to its genetic materials [24]. The lipid composition of these structures influences the virus's ability to effective entry for replication [25]. Evidence indicates the colocalization of DMVs and lipid droplets. SASR-CoV-2 can capture lipid material from lipid droplets. Non-structural Protein 6 (NSP6) mediates the association between DMV and lipid droplets by recruiting lipid droplet-tethering complex DFCP-1 for DMV formation [26].

Understanding these patterns and interactions are crucial since the level of these lipids could be closely monitored in clinical settings and could potentially serve as biomarkers for disease severity and progression, aiding in the identification of high-risk patients and the development of targeted therapeutic interventions. Furthermore, given the involvement of lipid metabolism in viral replication and host immune response, modulating lipid pathways could offer new avenues for developing antiviral therapies or interventions to mitigate the impact of COVID-19.

Once inside cytosol, energy-producing carbon metabolism, particularly glycolysis, is utilized in facilitating the replication and transcription of SARS-CoV-2. The virus's infection leads to enhanced glycolysis to meet the massive energy demands for viral replication. This shift is part of the Warburg effect, a commonly seen metabolic reprogramming in cancer cells. In this review, the author summarized that SARS-CoV-2 increases reactive oxygen species (ROS) production, altering host metabolism to favor glycolysis and the pentose phosphate pathway [27]. Such metabolic reprogramming not only supports viral replication but also contributes to COVID-19's pathogenesis through increased lactate production and metabolic competition with host cells [28].

Furthermore, there are studies that have found the presence of diabetes mellitus in patients with COVID-19 adds additional

complexity to the already altered metabolic processes. Diabetes affects both innate and adaptive immunity, and patients suffering from dual diseases exhibit elevated levels of inflammatory biomarkers, including C-reactive protein and interleukin 6 (IL-6), and are more prone to severe outcomes. The hyperglycemic environment can exacerbate inflammatory responses and impair immune function, highlighting the critical interplay between glucose metabolism alterations and COVID-19 severity [29,30].

Similar to lipid-based therapeutic strategies, several drugs targeting glycolysis have been explored to address the metabolic alterations driven by SARS-CoV-2: 2-Deoxy-D-glucose (2-DG) is a glucose analog that can be transported into cytosol by glucose transporters, however, lacking one hydroxy group on C2 hinders the function of one enzyme catalyzing former step in glycolysis, thereby halting this energy-producing pathways necessary for viral replication, further inhibits glycolysis by blocking the glycolytic pathway, thereby reducing the energy supply needed for viral replication. Through this mechanism, 2-DG offers good potential to starve the virus, and consequently, reduces viral load [31]; Metformin is a drug commonly used to treat type 2 diabetes. In addition to the aforementioned findings that preexisting conditions related to diabetes exacerbate host immunity among COVID-19 patients, metformin itself has been shown to have an inhibitory effect on enzymes that play crucial roles in the electron transport chain, such as NADH oxidoreductase [32]. Similarly, but not equivalently, this drug targets energy supply pathway for viral survival other than glycolysis, yet it is promising. Despite the supportive theories and clinical results [33], the mechanism of Metformin in alleviating disease severity remains unclear, and it even exhibits effect in a gender-dependent manner [34].

Beyond altering glucose processing, the virus also hijacks the host's one-carbon metabolism, a fundamental pathway for both nucleotide synthesis and post-translational modifications (PTMs), which are vital for both viral replication and host cell function [35]. Ribonucleic acid (RNA) capping is one of the PTMs SARS-CoV-2 employs. The mechanism is facilitated by S-adenosylmethionine (SAM)-dependent methylation and folate metabolism, producing methyl donor SAM to methylate the 7th nitrogen on guanosine, followed by adding this 7-methylguanosine (m7G), to 5′ end of the viral RNA via a triphosphate bridge. This strategy enables viruses for immune evasion, maintenance of RNA stability, and initiation of translation [36]. This highlights the potential for targeting these methyl group donors for therapeutic interventions. Specifically, drugs that disrupt S-adenosylmethionine (SAM) production demonstrates strong antiviral potency against SARS-CoV-2 [37], pointing to one-carbon metabolism as a critical area for further research and drug development.

Alteration of amino acid metabolism is also seen in SARS-Cov-2 infection, leading to a decrease in tryptophan levels and an increase in arginine and glutamine levels [38]. The respective changes may bring the following impacts: Neuropsychiatric symptoms observed in patients suffering from post-acute sequelae of COVID-19 (PASC), as tryptophan is a precursor for the synthesis of serotonin, playing significant role in regulating mood and behavior; Hyperinflammatory response observed in severe COVID-19 patient, as Arginine is involved in the synthesis of nitric oxide, a key mediator of immune responses that is produced by immune cells such as macrophages and it plays role in regulating inflammation; Affected nucleotide and amino acid synthesis and virus pathogenesis, as Glutamine is involved in several metabolic pathways, including the synthesis of mentioned molecules. In addition, glutamine is responsible for activation and proliferation of leucocyte B cells, T cells, and macrophages, and it regulates cytokine production [39]. Overall, the altered levels of these amino acids may contribute to the pathogenesis of COVID-19.

As outlined earlier, a significant number of COVID-19 survivors are suffering from PASC, a collection of long-term symptoms, including physical conditions (e.g., fatigue, dyspnea), and neuropsychiatric conditions (e.g., anxiety, depression) [40]. Research detailed in a paper titled "Accelerated biological aging in COVID-19 patients" demonstrates that SARS-CoV-2 infection substantially accelerates epigenetic aging compared to healthy individuals. Moreover, the severity of COVID-19 symptoms positively correlates with increased epigenetic aging and telomere shortening, both of which are indicated by altered deoxyribonucleic acid (DNA) methylation levels [41]. Crucially, alterations in metabolic processes due to SARS-CoV-2 infection, including disrupted lipid and glucose metabolism, can impact DNA methylation patterns. These metabolic changes produce metabolites such as methionine that are shared with one-carbon metabolism, thereby modulating the availability of S-adenosylmethionine (SAM), the primary methyl donor for DNA methylation, such changes affect the enzymatic kinetics of DNA methyltransferases, the enzyme catalyze DNA methylation, by altering the availability of the substrate, thereby influencing gene expression and contributing to the aging process. Additionally, metabolic alterations, as described earlier, can lead to increased inflammatory responses, which are known to induce senescence associated secretory phenotype (SASP) [41,42], and affect DNA methylation patterns, potentially exacerbating the acceleration of epigenetic aging and contributing to the complexity and diversity of PASC symptoms.

Summarizing the findings of this review, SARS-CoV-2 infection induces significant metabolic reprogramming, particularly in lipid and glucose metabolism, along with one-carbon and amino acid metabolisms. The intricate interplay among these changes induces cellular stress and cell senescence by manipulating DNA methylation levels, causing accumulative epigenetic aging and telomere shortening. Reasonably, elevating severity of symptoms and risk of developing long COVID. These changes not only elucidate the

virus's ability to exploit host cellular mechanisms at multiple stages of its life cycle for replication and pathogenesis, but also highlight potential therapeutic targets within these pathways. Specifically, several lipid-modulating and glucose-modulating drugs offer alternative paths in combating COVID-19 infection and long-term complications. Furthermore, the virus's dependency on one-carbon metabolism offers additional path for therapeutic intervention. Targeting these metabolic alterations presents a promising strategy for developing effective COVID-19 treatments.

However, effects of metabolic alterations are highly context-based and cannot be generalized for developing therapeutic strategies. For instance, in a study titled "Circulating Immune Bioenergetic, Metabolic, and Genetic Signatures Predict Melanoma Patients' Response to Anti–PD-1 Immune Checkpoint Blockade," metabolic reprogramming, particularly, glycolysis and lipid metabolites were enhanced to support better responses to immunotherapy in melanoma patients [43], which contrasts with the observations in SARS-CoV-2 infection, which primarily supports the pathogen replication and immune evasion.

Therefore, understanding the contextual metabolic alterations in various diseases is necessary and a continuous process, but it offers promising opportunities for therapeutic intervention. Moreover, monitoring these changes could provide biomarkers for disease severity and progression diagnosis, aiding in identifying high-risk patients [43]. As the world continues to grapple with the challenges posed by COVID-19 and the virus actively mutates, insights from this review and other relevant research are invaluable in guiding effective treatment strategies, understanding the broader implications of viral-host interactions, and emphasizing the need for continued research.

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