The roles of lipids in SARS-CoV-2 viral replication and the host immune response

Katherine N. Theken\textsuperscript{1,2,3}, Soon Yew Tang\textsuperscript{1,2}, Shaon Sengupta\textsuperscript{2,4}, and Garret A. FitzGerald\textsuperscript{1,2,5,*}

\textsuperscript{1}Department of Systems Pharmacology and Translational Therapeutics, and \textsuperscript{2}Institute for Translational Medicine and Therapeutics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; \textsuperscript{3}Department of Oral Surgery and Pharmacology, University of Pennsylvania School of Dental Medicine, Philadelphia, PA, USA; \textsuperscript{4}Department of Pediatrics, and \textsuperscript{5}Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Abstract

The significant morbidity and mortality associated with severe acute respiratory syndrome coronavirus 2 infection has underscored the need for novel antiviral strategies. Lipids play essential roles in the viral life cycle. The lipid composition of cell membranes can influence viral entry by mediating fusion or affecting receptor conformation. Upon infection, viruses can reprogram cellular metabolism to remodel lipid membranes and fuel the production of new virions. Furthermore, several classes of lipid mediators, including eicosanoids and sphingolipids, can regulate the host immune response to viral infection. Here, we summarize the existing literature on the mechanisms through which these lipid mediators may regulate viral burden in COVID-19. Furthermore, we define the gaps in knowledge and identify the core areas in which lipids offer therapeutic promise for severe acute respiratory syndrome coronavirus 2.

Supplementary key words lipidomics • lipid metabolism • cholesterol • eicosanoids • phospholipids • sphingolipids • viral infection • COVID-19 • coronavirus • SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 190 million people and accounted for over 4 million deaths worldwide in this pandemic. This public health challenge has underscored the need to limit viral replication and manage the immunological response to infection. Initially thought of as a respiratory pathogen, it is now well accepted that COVID-19 leads to multisystem dysfunction, including considerable cardiovascular, renal, and central pathology, as well as thrombotic and vascular complications.

While the COVID-19 pandemic is a global public health crisis of unprecedented proportions, even before this, seasonal infections with influenza and other viral pathogens were responsible for significant morbidity and mortality. While each pathogen has its unique characteristics that contribute to pathology and host response, they share some common features. Most viral respiratory infections, except for adenoviruses, are caused by RNA viruses. This includes influenza viruses, coronaviruses, respiratory syncytial virus (RSV), human metapneumovirus, paramyxoviruses, and rhinoviruses. Symptoms might range from mild upper respiratory illness to acute respiratory distress syndrome (ARDS). In most cases, the virus is limited to the upper respiratory tract, spreading to the more distal alveolar epithelium in severe infection. The host must either reduce the pathogen burden (antiviral resistance) or control the adverse effects of the infection on the host's health (disease tolerance) to overcome the infection. Unfortunately, in the process of mounting an effective antiviral response, several proinflammatory signaling cascades are activated. The host may clear the virus only to succumb to the tissue damage that is sustained because of the antiviral response. Host tolerance pathways, on the other hand, may act to suppress the immune response to limit inflammation-induced damage to the host.

Viruses interact with lipid membranes to infect a cell and reprogram lipid metabolism to fuel replication. Furthermore, viral infection stimulates the production of bioactive lipid mediators that mediate the host immune response—both by inducing more inflammation and by regulating the tissue damage. The aim of this review is to summarize our knowledge with a view to elucidating the role of lipids in the pathophysiology of COVID-19, thus highlighting the gaps in knowledge and therapeutic opportunities.

LIPIDS IN VIRAL ENTRY

As obligate intracellular pathogens, viruses interact with host lipids throughout their life cycle (Fig. 1). While many of the pathways involved are specific to a particular virus or family of viruses, others generalize across multiple families of viruses and thus may be potential targets for development of broad-spectrum antiviral agents. There are many reviews summarizing...
the role of lipids in viral entry and replication (1–5). Here, we highlight a few examples with emphasis on SARS-CoV-2 and other coronaviruses.

Viruses use various strategies to cross the plasma membrane to enter the host cell. Some nonenveloped viruses can induce membrane lysis, generate pores, or hijack cellular transport vesicles to enter target host cells (6). Other viruses enter host cells via apoptotic mimicry by incorporating phosphatidylserine into their lipid envelopes, as external presentation of this phospholipid is an apoptotic signal for phagocytes to initiate cell clearance (7). Most enveloped viruses infect host cells via either direct fusion of their envelopes with plasma membranes or receptor-mediated endocytosis (8). In the case of SARS-CoV and SARS-CoV-2, viral fusion is initiated by binding of the viral spike (S) protein to angiotensin-converting enzyme 2 (ACE2). This is followed by proteolytic cleavage at the S1/S2 boundary by transmembrane serine protease 2 at the plasma membrane or cathepsins in the lysosome, inducing a conformational shift in the S2 subunit that interacts with the membrane to promote viral fusion (9, 10). For SARS-CoV, it has been shown that the S protein must be palmitoylated to interact with the host membrane and promote viral fusion (11, 12). Similarly, S-acylation of the S protein by ZDHHC20 is essential for SARS-CoV-2 infectivity, stabilizing the S protein and facilitating its interaction with lipid bilayers (13). Thus, the host ZDHHC enzymes that catalyze the S-acylation of viral proteins may be potential drug targets (14).

Viruses can also utilize lipoprotein receptors to enter the host cell. This has been extensively studied for hepatitis C virus, which can enter cells via the LDL receptor or the HDL receptor scavenger receptor B type 1 (SR-B1) (1, 15, 16). It has also been reported that the SARS-CoV-2 S protein can bind cholesterol in HDL particles, and that uptake of HDL by SR-B1 facilitates viral entry into cells that coexpress the ACE2 receptor (17). Blocking SR-B1 prevents SARS-CoV-2 infection in multiple cell types in vitro (18).

The success of the fusion process also depends upon the composition of the viral envelope and host membrane because the biophysical properties of the various lipid species affect membrane fluidity and curvature. For example, phosphatidylethanolamine and cholesterol enhance membrane fluidity and promote negative curvature that are critical for viral fusion, while lysophospholipids (LPLs) promote positive curvature and inhibit fusion (19). Thus, agents that modify the lipid content of the viral envelope may have utility as broad-spectrum antivirals. One such compound, LJ001, is a membrane-intercalating photosensitizer that exhibits antiviral activity in vitro. Upon light activation, LJ001 generates singlet oxygen that oxidizes unsaturated phospholipids to enhance membrane rigidity and decrease viral fusion (20). Although both the viral envelope and host cell membranes would become oxidized in the presence of LJ001, the host cell can synthesize new lipids to repair its membrane, while the viral envelope is static, which enhances specificity for the virus and prevents cytotoxicity (21). The utility of LJ001 in vivo is limited because of its need for photoactivation and poor pharmacokinetic properties, but it may serve as a lead compound for the development of...
novel antivirals with a similar mechanism of action (20). Another potential class of broad-spectrum antiviral compounds that target lipid membranes includes rigid amphipathic fusion inhibitors, nucleoside analogs that intercalate in lipid membranes and inhibit the formation of negative curvature (22). Most importantly, in contrast to fusion inhibitors that target viral proteins (23), fusion inhibitors that act on lipid membranes would theoretically exhibit broader antiviral activity with less potential for development of resistance.

Lipid rafts, discrete membrane microdomains enriched in cholesterol and glycosphingolipids, contain high concentrations of cell surface receptors and can serve as platforms to localize the endocytosis machinery. Consequently, they play an important role in facilitating viral entry (24). Depletion of cholesterol with methyl-β-cyclodextrins decreases viral entry for several coronaviruses, including mouse hepatitis virus (25, 26), avian infectious bronchitis virus (27), and SARS-CoV (28–30). ACE2 has also been shown to colocalize with lipid rafts in host cell membranes (29, 30), although this has been disputed (28). Although glycosphingolipids can function as coreceptors for some viruses (e.g., HIV (31, 32) and influenza A virus (IAV) (33, 34)), this has not been observed for SARS-CoV-2 or other coronaviruses. Sphingomyelin in lipid rafts can be hydrolyzed by acid and neutral sphingomyelinases to ceramide, a lipid that promotes negative curvature and enhances membrane fluidity. Ceramide molecules self-associate to create ceramide-enriched membrane platforms, which cluster receptors and are involved in cell signaling and membrane trafficking (3, 35, 36). Thus, some viruses exploit ceramide-enriched membrane platforms, as in the case of rhinoviruses that activate acid sphingomyelinase to facilitate entry into the cell (37, 38).

In addition to their role in mediating viral fusion, lipids can affect viral entry by altering conformation of either the host or viral receptor. Inhibition of the serine palmitoyltransferase complex, which catalyzes the first and rate-limiting step in de novo ceramide and sphingolipid biosynthesis, altered the conformation of the murine norovirus receptor (CD300I) such that the virus was unable to bind and infect the cell. This effect was reversed by addition of exogenous ceramide (39). Similarly, a recent study demonstrated that the SARS-CoV-2 S protein tightly binds the free fatty acid, linoleic acid (LA). This binding stabilizes the S protein in a locked conformation and reduces its interaction with the ACE2 receptor. A similar fatty acid–binding pocket was also observed in SARS-CoV and Middle East respiratory syndrome related coronavirus (MERS-CoV) (40). It has also been reported that omega-3 fatty acids, including LA and eicosapentaenoic acid (EPA), can interact with the receptor-binding domain of the SARS-CoV-2 S protein and inhibit attachment to the ACE2 receptor in vitro (41).

LIPIDS IN VIRAL REPLICATION

Upon entering the host cell, viruses reprogram cellular metabolism to remodel cellular membranes and fuel production of new virions (5, 42). Positive-sense RNA viruses assemble membrane-enclosed replication organelles (ROs), which localize the viral replicate and cofactors in close proximity and may shield the virus from immune recognition (1). The composition and source of lipids to form ROs varies among different families of viruses (2, 5). However, recruitment of phosphatidylinositol 4-kinase IIIβ appears to be a common strategy for remodeling cellular membranes, as this enzyme is important for the formation of ROs for human rhinovirus (HRV, RV-A16) (43), Aichi virus (44), Coxsackie B virus, and hepatitis C virus (45). In contrast, West Nile virus and dengue virus rely on fatty acid synthase to alter the lipid content at the replication membranes (46, 47).

Several studies have demonstrated that coronavirus ROs are derived from the endoplasmic reticulum (48–51), and for SARS-CoV, the viral nonstructural proteins nsP3, nsP4, and nsP6 are involved in RO formation (52). Recent evidence suggests that cytosolic phospholipase A2α, which cleaves phospholipids at the sn-2 position to release LPLs and arachidonic acid (AA), is involved in coronavirus RO formation. Inhibition of cytosolic phospholipase A2α decreased LPL release, which decreased the formation of double membrane vesicles and impaired replication of HCoV-299E and MERS-CoV in vitro (53). Similarly, HCoV-299E infection in Huh-7 cells in vitro increased the levels of LPLs, specifically lysophosphatidylcholines and lysophosphatidylethanolamines, and fatty acids, including AA and LA, which the authors attributed to activation of cPLA2. Interestingly, addition of exogenous AA or LA decreased replication of both HCoV-299E and MERS-CoV, but it was not determined whether this was due to downstream lipid mediators generated from these fatty acids or activation of the Lands cycle that converts LPLs to phospholipids (54).

Several studies indicate that cholesterol homeostasis plays a critical role in coronavirus infection. MERS-CoV infection in vitro enhanced accumulation of lipid droplets and cholesterol and upregulated genes involved in lipid biosynthesis by activating SREBPs. Inhibition of SREBP DNA-binding activity with AM580 decreased viral replication in vitro. AM580 treatment in vivo decreased viral titers, improved survival, and decreased lung histopathology in mice infected with MERS-CoV or H7N9 IAV (55). Multiple genetic screens have also identified cholesterol biosynthesis as a key pathway in SARS-CoV-2 infection (56–60). SREBP-2, SREBP cleavage-activating protein, membrane-bound transcription factor site-1 protease, and membrane-bound transcription factor site-2 protease were consistently observed as critical host factors, and other genes linked to cholesterol metabolism and trafficking,
including LDL receptor, NPC intracellular cholesterol transporter 1 (NPC1), NPC intracellular cholesterol transporter 2, and ER membrane protein complex subunit 1, were enriched in screens of SARS-CoV-2, HCoV-229E, and HCoV-OC43 infection (56, 59, 60). NPC1 has been shown to play a role in replication for multiple viruses, including Ebola virus, HIV, and Chikungunya virus thus, NPC1 inhibition has been proposed as a potential antiviral strategy in COVID-19 (61).

SARS-CoV-2 infection in monocytes increased lipid droplet formation and upregulated genes involved in lipid metabolism, including CD36, PPAR-γ, SREBP-1, and diacylglycerol acyltransferase-1. Inhibition of diacylglycerol acyltransferase-1 with A922500 dose-dependently reduced viral load in primary human monocytes and inhibited viral replication in Vero E6 cells. Viral particles colocalized with lipid droplets, predominantly associated with the phospholipid monolayer, suggesting that lipid droplets may serve as a replication platform for SARS-CoV-2 (62). Taken together, these results indicate that targeting SREBP signaling might be a viable therapeutic approach to utilize against multiple coronaviruses.

Genetic screens also highlight the importance of lysosomes and autophagy in the SARS-CoV-2 life cycle, potentially via their roles in lipid trafficking and metabolism. In addition to NPC1 and NPC intracellular cholesterol transporter 2, which have well-recognized roles in cholesterol transport in the lysosome, TMEM41B was identified as a critical host factor required for replication of multiple coronaviruses, including SARS-CoV-2 (59, 63). Although this protein has not been well characterized, it has been shown to regulate autophagy and lipid metabolism; TMEM41B-deficient cells exhibit impaired autophagosome formation, enlarged lipid droplets, and reduced β-oxidation of fatty acids (64, 65). In the case of SARS-CoV-2 infection, it has been hypothesized that TMEM41B facilitates ER membrane remodeling to form ROs (59, 63). Sigma-1 and sigma-2 receptors, both of which appear to play roles in cholesterol transport (66, 67), were identified as potential targets in SARS-CoV-2-human protein–protein interaction screens (68, 69). In screens of repurposed drugs, it has been observed that there was a strong correlation between antiviral efficacy against SARS-CoV-2 and the magnitude of phospholipidosis in vitro (70). However, none of the lead compounds tested exhibited significant antiviral activity in vivo, underscoring the need for additional research to translate these in vitro observations into a useful therapeutic approach in humans.

LIPIDS IN REGULATING THE IMMUNE RESPONSE TO VIRAL INFECTION

Eicosanoids are immunomodulatory and may also impact viral replication and the host antiviral response. These lipid mediators include prostaglandins (PGs) and thromboxane (Tx)–together, prostanoids–formed by the PG synthase enzymes, known as cyclooxygenases (COXs)-1 and COX-2; the leukotrienes, hydroperoxy and hydroxy fatty acids formed by the lipoxygenase (LOX) enzymes (5-LOX, 12-LOX, 15-LOX); and epoxyeicosatrienoic acids and 20-hydroxyeicosatetraenoic acid formed by cytochrome P450 enzymes. Targeting these pathways has been proposed as a strategy to dampen cytokine storm and treat complications of SARS-CoV-2 infection (71-75).

Genetic deletion or pharmacologic inhibition of COX-2 decreases pulmonary inflammation and improves mortality in mouse models of IAV infection (74-78). Interestingly, mortality was higher in COX-1−/− mice (74) and mice treated with the COX-1 selective inhibitor SC560 (75), relative to controls. However, the mechanism by which selective COX-1 inhibition may worsen outcomes in IAV infection was not investigated, and the relative effects of nonselective versus COX-2 selective nonsteroidal anti-inflammatory drugs have not been delineated. COX-2 inhibition may enhance the early antiviral response after IAV infection in the setting of a chronic inflammatory state such as that induced by obesity (79). Although diet-induced obese mice had higher levels of cytokines and chemokines in lung homogenates at baseline, they displayed poor induction of type 1 interferon responses early in the course of infection and were subsequently unable to clear the virus. Acetaminophen treatment before IAV infection not only restored the early type 1 interferon induction in obese mice but also improved survival on day 14 after infection. Of note, no significant differences in survival due to acetaminophen were observed in lean mice after IAV infection (79).

Of the individual prostanooids, PGE2 and PGD2 have been most studied in the context of viral infection. Inhibition of PGE2 enhanced antiviral immunity and improved survival after IAV infection in mice. Compared with wild-type controls, mice lacking the microsomal PGE synthase-1 (Ptges−/−) had lower viral loads and greater infiltration of macrophages, monocytes, and dendritic cells (DCs) into their lungs and BALF 3 days after infection. After IAV infection in vitro, bone marrow–derived macrophages from Ptges−/− mice produced more interferon-β and had increased apoptosis than infected wild-type bone marrow–derived macrophages. This difference was abrogated by addition of exogenous PGE2, but not other prostanooids, and was mediated through its receptors, EP2 and EP4. Furthermore, Ptges−/− mice exhibited a more robust adaptive immune response, with higher levels of CD4+ and CD8+ T cells in lymph nodes, BALF, and lung on days 9 and 11 after infection. Finally, pharmacologic inhibition of microsomal PGE synthase-1 or EP2 and EP4 signaling in vivo improved survival after IAV infection, and this benefit was lost in mice lacking the interferon-α/β receptor. These results indicate that PGE2 suppresses the innate and adaptive
immune response to IAV infection in a type I interferon–dependent manner (80). A recent study reported a host-coronavirus protein interaction between PGE2 synthase 2 and nsp7 that was conserved among MERS-CoV, SARS-CoV, and SARS-CoV-2 (68), but whether this interaction impacts viral replication has yet to be elucidated.

Several studies suggest that PGD2 plays a role in the immune response to respiratory viral infections as well. DPRI signaling delays migration of DCs to the lung and lymph nodes via downregulation of the chemokine CCR7 (81, 82). Interestingly, the impact of DPRI signaling and delayed DC migration on adaptive immune responses appears to be age dependent. DPRI inhibition enhanced DC migration and T-cell proliferation and increased survival in older mice (12 months of age), but not in young mice (6 weeks of age), after SARS-CoV and IAV infection (82). PGD2 also contributes to the pathogenesis of RSV bronchiolitis and susceptibility to asthma via DPRI signaling (83). In a neonatal model of severe RSV bronchiolitis, treatment with a DPRI inhibitor decreased viral load and improved morbidity via upregulation of IFN-α. This effect was recapitulated by treatment with a DPRI agonist, suggesting that these two receptors for PGD2 have opposing roles in the regulation of the antiviral response.

Prostacyclin (PGI2) can regulate the inflammatory response but has not been well studied in context of viral infection. We examined the role of PGI2 in RSV infection using mice lacking the IP receptor (IPr) or overexpressing prostacyclin synthase in alveolar and airway epithelial cells (84). Mice overexpressing prostacyclin synthase in alveolar and airway epithelial cells displayed less weight loss and lower viral titers after RSV infection than the littermate controls. In contrast, mice lacking the IPr lost more weight and had higher viral titers, suggesting that PGI2 may enhance the antiviral response and improve viral clearance.

While neither PGF2α nor TxA2 have been investigated with respect to modulation of viral clearance or host response to viral infection, they may yet contribute to the consequences of viral infection in the lung. For example, PGF2α accelerates the fibrotic reaction to bleomycin and might contribute to this consequence of viral infection (85). More directly, we have shown that antagonism of the thromboxane receptor prevents evolution of ARDS in a lipopolysaccharide model in sheep (86). In the case of COVID-19, suppression of TxA2 formation may have the added benefit of platelet inhibition (87), and multiple trials of low-dose aspirin at various stages in patients with COVID-19 are ongoing (Table 1).

With regard to the LOX pathway, studies suggest that LTβ4 is protective, whereas the cysteinyl leukotrienes (cysLTs), LTC4, LTD4, and LTE4 worsen outcomes after viral infection. LTβ4 elicits antiviral activity in both in vitro and in vivo models of viral infections by promoting release of antimicrobial peptides (89–91) and stimulating interferon production via activation of the nucleotide-binding oligomerization domain–containing protein 2 pathway (92). In mice infected with IAV, LTβ4 administration 24 h after infection reduced viral load and lung injury (90). In addition to enhancing the antiviral response, there is also evidence that LTβ4 promotes disease tolerance to IAV infection. LTβ4 signaling through the BLT1 increased susceptibility of type I alveolar epithelial cells to IAV infection, and treatment with the BLT1 antagonist, zafirlukast, improved survival (94). CysLT1 blockade decreased airway hyper-responsiveness in mice challenged with RSV (95) and attenuated airway hyper-responsiveness, infiltration of inflammatory cells, and excessive mucus production upon reinfection (96). A retrospective analysis in hospitalized patients with COVID-19 reported that the risk of clinical deterioration, defined as any increase in the COVID-19 ordinal scale value from day 1 to day 3 of hospitalization, was significantly lower in patients treated with montelukast than in patients not receiving montelukast (97). Several prospective clinical trials are underway to explore the utility of CysLT1 antagonists in treating COVID-19 (Table 1).

The epoxyeicosatrienoic acids possess potent anti-inflammatory properties by attenuating cytokine-induced NF-κB activation and leukocyte adhesion to the vascular wall (98), and inhibition of soluble epoxide hydrolase has been studied as a therapeutic strategy to decrease inflammation in vivo (99). Conversely, 20-hydroxyeicosatetraenoic acid activates NF-κB signaling and induces expression of cellular adhesion molecules and cytokines, thereby promoting inflammation (100). However, the role of these cytochrome P450–derived eicosanoids in regulating the host response to viral infection has not been studied to date (71).

The omega-3 fatty acids EPA and DHA have also been suggested as possible anti-inflammatory therapeutics for COVID-19. The anti-inflammatory effects of omega-3 fatty acids have been attributed by some to the formation of specialized proresolving mediators. However, this is controversial, and we find no evidence of their formation in biologically relevant quantities in humans (101). An observational study reported that a higher omega-3 index, EPA + DHA as a percentage of total erythrocyte fatty acids, was inversely associated with the risk of death in 100 hospitalized patients with COVID-19 (102). Results of a pilot study of EPA + DHA supplementation (103) and a case report of icosapent ethyl treatment (104) in patients with COVID-19 also suggest benefit, and additional prospective clinical trials are ongoing (Table 1).
LIPIDOMICS OF COVID-19

Several studies have performed lipidomic profiling in patients with COVID-19. Although there is heterogeneity among these studies regarding the analytical methods used and the patient populations, some consistent findings have been reported, particularly with regard to serum cholesterol and lipoproteins. Serum triglycerides and VLDL are significantly higher, whereas HDL and LDL are significantly lower in patients with COVID-19 than in age- and sex-matched healthy controls (105–109). Interestingly, several observational studies have demonstrated that statins may improve outcomes in patients with COVID-19 (110, 111), providing support for future studies to evaluate treatment with these drugs prospectively and investigate the mechanisms underlying such a beneficial effect.

Metabolomic and transcriptomic profiling also indicates a shift to fatty acid oxidation in patients with COVID-19 compared with healthy controls, which may indicate a metabolic switch to fuel viral replication (105, 112). However, similar alterations in serum lipoproteins and lipid metabolism have also been reported in patients with trauma (113), ARDS (114), and other infections (115), suggesting that the dysregulation of lipid metabolism observed in patients with COVID-19 reflects a common metabolic shift in response to critical illness, rather than a unique signature of SARS-CoV-2 infection. Most studies report that the levels of HDL and LDL return to baseline after recovery. However, some studies suggest that alterations in lipid metabolism persist even after recovery from COVID-19 (116, 117), and it has been reported that lipid metabolism is dysregulated in survivors of SARS 12 years after...
infection, compared with age-matched healthy volunteers (118). Thus, longitudinal studies in patients who recover from COVID-19 will be instrumental in determining how long these alterations in lipid metabolism persist or if they are associated with long-term sequelae of infection.

Sphingosine-1-phosphate (SIP), a metabolite of sphingosine that can act intracellularly or via one of five G-protein-coupled receptors (SIP1 to SIP5), is decreased in patients with COVID-19 compared with healthy controls (119, 120). HDL is the major carrier for SIP in the plasma; thus, this decrease may be a consequence of the decrease in HDL levels in patients with COVID-19, as has been previously reported in patients with sepsis (121). SIP signaling can modulate numerous biological processes, including cell proliferation, apoptosis, and inflammation. In mouse models of IAV infection, activation of the SIP1 receptor in the lung endothelium restrained cytokine storm, reduced lung pathology, and improved survival (122–125), while genetic deletion of SIP1 in endothelial cells decreased survival and worsened lung pathology (125).

In addition of the immunomodulatory effects of SIP signaling, inhibition of the sphingosine kinases (SK1 and SK2) that phosphorylate sphingosine to SIP may have antiviral activity. In the context of IAV infection, SK1 and SK2 promote viral replication by modulating NF-kB activation (126–128). Conversely, overexpression of SIP lyase, which irreversibly cleaves SIP to phosphoethanolamine and hexadecanial, inhibited viral protein synthesis, and decreased IAV viral titers in vitro (126, 129). SK inhibition suppresses viral protein and RNA synthesis by decreasing IKKαβ phosphorylation and NF-kB activation. SK inhibition also decreases activation of the ERK MAPK and PI3K/AKT signaling pathways, leading to decreased phosphorylation of RanBP3 and decreased nuclear export of viral RNP complexes (127). Moreover, treatment with SK2 inhibitor (opaganib) in mice in vivo decreased viral titers, blunted weight loss, and decreased mortality after IAV infection (treated: 50% vs. control: 90%). Similar improvements in survival were also observed with SK1 inhibitor treatment (128). Of note, studies of opaganib in patients with SARS-CoV-2 pneumonia are ongoing (Table 1).

Patients with COVID-19 also exhibited lower levels of glycerophospholipids (107, 119, 120) and higher levels of the corresponding LPLs (107, 120), indicating increased phospholipase A2 activation. Moreover, expression of enzymes involved in eicosanoid synthesis (PLA2G4A, PTGS2, PTGES3, ALOX5, and ALOX5AP) was upregulated in peripheral blood mononuclear cells of patients with COVID-19 (130). Consistent with these observations, higher levels of AA and oleic acid (107) and alterations in eicosanoid profiles (131) have also been reported in patients with COVID-19. A recent report suggests that levels of a secretory PLA2 may be a biomarker predictive of severe COVID-19 (132). Further investigation is warranted to determine whether drugs that modulate eicosanoid lipid mediators might have antiviral activity in COVID-19.

CONCLUSIONS

The integral role of lipids in the viral life cycle suggests that targeting these pathways may be a viable therapeutic strategy. However, development of such novel antiviral agents for COVID-19 will require a better understanding of the effects of SARS-CoV-2 infection on lipid metabolism in vitro and in model organisms. Furthermore, serial lipidomic analyses in individuals with COVID-19 may identify specific lipid pathways that mediate the heterogeneous response to viral infection, serve as prognostic biomarkers, or contribute to long-term sequelae.24

Author contributions

K. N. T., S. Y. T., and S. S. writing – original draft; K. N. T., S. Y. T., S. S., and G. A. F. writing – review and editing.

Funding and additional information

This work was supported by the National Institutes of Health (Grant number K08HL132053 to S. S.) and U54TR001878. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest

The authors declare that they have no conflicts of interest with the contents of this article.

Abbreviations

AA, arachidonic acid; ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; cysteLT, cysteinyl leukotriene; DC, dendritic cell; EPA, eicosapentaenoic acid; IAV, influenza A virus; IPr, IP receptor; LA, linoleic acid; LOX, lipoygenase; LPL, lysophospholipid; MERS-CoV, Middle East respiratory syndrome coronavirus; NPCI, NPC intracellular cholesterol transporter 1; PG, prostaglandin; PGI2, prostacyclin; RO, replication organelle; RSV, respiratory syncytial virus; S, spike; SIP, sphingosine-1-phosphate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SK, sphingosine kinase; SR-BI, scavenger receptor B type 1; Tx, thromboxane.

Manuscript received April 1, 2021, and in revised from September 1, 2021. Published, JLR Papers in Press, September 29, 2021, https://doi.org/10.1016/j.jlr.2021.100129

REFERENCES

1. Heaton, N. S., and Randall, G. (2011) Multifaceted roles for lipids in viral infection. Trends Microbiol. 19, 368–375

2. Ketter, E., and Randall, G. (2019) Virus impact on lipids and membranes. Annu. Rev. Virol. 6, 319–340

3. Bezgoyev, J., Gulbins, E., Friedrich, S. K., Lang, K. S., and Duhon, V. (2018) Sphingolipids in early viral replication and innate immune activation. Biol. Chem. 399, 1115–1123
4. Schoggins, J. W., and Randell, C. G. (2013) Lipids in innate antiviral defense. Cell Host Microbe. 14, 379–385
5. Zhang, Z., He, G., Filipowicz, N. A., Randall, G., Belov, G. A., Kopek, B. G., and Wang, X. (2019) Host lipids in positive-strand RNA virus genome replication. Front. Microbiol. 10, 286
6. Cossart, P., and Helenius, A. (2014) Endocytosis of viruses and bacteria. Cold Spring Harb. Symp. Quant. Biol. 79, 81–92
7. Moller-Tank, S., and Maury, W. (2014) Phosphatidylserine receptors: enhancers of enveloped virus entry and infection. Virology. 468–470, 565–580
8. Lanrein, M., Schlegel, A., and Kempf, C. (1994) Entry and uncoating of enveloped viruses. Biochem. J. 302, 313–320
9. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Kruger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Muller, M. A., Drosten, C., and Pohlhann, S. (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 181, 271–280.e29
10. Shang, J., Wan, Y., Luo, C. Ye, G., Geng, Q., Auerbach, A., and Li, F. (2020) Cell entry mechanisms of SARS-CoV-2. Proc. Natl. Acad. Sci. U. S. A. 117, 11727–11734
11. McBride, C. E., and Machamer, C. E. (2010) Palmitoylation of SARS-CoV S protein is necessary for partitioning into detergent-resistant membranes and cell-cell fusion but not interaction with M protein. Virology. 405, 139–148
12. Petit, C. M., Choulenko, V. N., Iyer, A., Colgrove, R., Farzan, M., Knipe, D. M., and Koussoula, K. G. (2007) Palmitoylation of the cysteine-rich endodomain of the SARS-coronavirus spike glycoprotein is important for spike-mediated cell fusion. Virology. 360, 264–274
13. Mestia, P. S., Abiham, L., Sergeeva, O., Turelli, P., Kunz, B., Raclot, C., Montoya, J. P., Abiham, L. A., Peraro, M. D., Akyol Ataman, Z., Holzinger, S., Belouzard, S., Dubuisson, J., Solund, C., Weis, N., Gottwein, B. G., and Wang, X. (2019) Host lipids in positive-strand RNA virus genome replication. Proc. Natl. Acad. Sci. U. S. A. 116, 12766–12771
14. Drexel, M., Dao Thi, V. L., Fresquet, J., Guerin, M., Julia, Z., Verney, G., Durantel, D., Zouloum, F., Lavillette, D., Cosset, F. L., and Bartosch, B. (2009) Receptor complementation and mutagenesis reveal SR-BI as an essential HCV entry factor and enhancer of enveloped virus entry and infection. Annu. Rev. Biochem. 78, 1253–1283
15. Wess, S., Sparks, J. R., Yoon, Q. W., Yang, X., Zhang, G., and Zhang, Q. X. (2020) SARS-CoV-2 entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. Cell Res. 28, 290–301
16. Li, G. M., Li, Y. G., Yamate, M. L. S., Belouzard, S., Dubuisson, J., Solund, C., Wu, N. H., Kopek, B. G., and Wang, X. (2019) Host lipids in positive-strand RNA virus genome replication. Proc. Natl. Acad. Sci. U. S. A. 116, 12771–12776
17. Foley, T., Groll, A., Groll, A., and Hourcade, D. (2000) Receptor complementation and mutagenesis reveal SR-BI as an essential HCV entry factor and functionally imply its intra- and extra-cellular domains. PLoS Pathog. 5, e1000510
18. Wei, D., Yuan, X., Yuan, Q., Wang, X., Zhang, J., Yang, X., Zhang, Y., Fan, C., Li, D., Deng, Y., Sun, J., Gong, J., Yang, X., Wang, Y., Wang, X., et al. (2020) HDL-scavenger receptor B type 1 facilitates SARS-CoV-2 entry. Nat. Metab. 2, 1891–1400
19. Ramirez, S., Fernandez-Antunez, C., Galli, A., Underwood, A., Pham, L. V., Ryberg, L. A., Feng, S., Pedersen, M. S., Mikkelsen, L. S., Belouzard, S., Dubuisson, J., Solund, C., Weis, N., Gottwein, J. M., Fahnoe, U., et al. (2021) Overcoming culture restriction for SARS-CoV-2 in human cells facilitates the screening of compounds inhibiting viral replication. Antimicrob. Agents Chemother. 65, e0097221
20. Teissier, E., and Pecheur, E. I. (2007) Lipids as modulators of membrane fusion mediated by viral fusion proteins. Env. Biochem. J. 36, 887–899
21. Vigant, F., Lee, J., Hollmann, A., Tanner, L. B., Akyol Ataman, Z., Yun, T., Shui, G., Aguilar, H. C., Zhang, D., Guo, F., Yang, P., Liu, K., Guan, M., and Tam, J. P. (2020) A broad-spectrum antiviral targeting entry of SARS-CoV-2 (previously 2019-nCoV) by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell. 180, 343–355
22. Lu, Y., Liu, D. X., and Tam, J. P. (2008) Lipid rafts are involved in SARS-CoV entry into Vero E6 cells. Biochem. Biophys. Res. Commun. 369, 344–349
23. Puri, A., Rawat, S. S., Lin, H. M., Finneegan, C. M., Mikovits, J., Roemmele, F. W., and Blumenthal, R. (2004) An inhibitor of glycosphingolipid metabolism blocks HIV-1 infection of primary T-cells. AIDS. 18, 485–498
24. Maguer-Chatinet, A., Yu, H., Garcia, S., Ducloux, E., Terris, B., and Bomsel, M. (2007) Galactosyl ceramide expressed on dendritic cells can mediate HIV-1 transfer from monocyte-derived dendritic cells to autologous T cells. Virology. 362, 67–74
25. Wiley, D. C., and Skehel, J. J. (1987) The structure and function of the hemagglutinin membrane glycoprotein of influenza virus. Annu. Rev. Biochem. 56, 365–394
26. Matsuoka, T., Sumi, M., Kubota, H., Taki, T., Okahata, Y., and Sato, T. (2009) Inhibition of influenza virus infections by sialyllectose-binding peptides selected from a phage library. J. Med. Chem. 52, 4247–4256
27. Grassme, H., Riethmuller, J., and Gubins, E. (2007) Biological aspects of ceramide-enriched membrane domains. Prog. Lipid Res. 46, 161–170
28. Zhang, Y., Li, X., Becker, K. A., and Gubins, E. (2009) Ceramide-enriched membrane domains—structure and function. Biochim. Biophys. Acta. 1788, 178–183
29. Drescher, S., Franz, P., Dumritu, C., Wilker, B., Jahnke, K., and Gubins, E. (2007) Infections with human rhinovirus induce the formation of distinct functional membrane domains. Cell Physiol. Biochem. 20, 241–254
30. Grassme, H., Richie, U., Wilker, B., and Gubins, E. (2005) Rhinoviruses infect human epithelial cells via ceramide-enriched membrane platforms. J. Biol. Chem. 280, 26256–26262
31. Orchard, R. C., Wilen, C. B., and Virgin, H. W. (2018) Sphingolipid biosynthesis induces a conformational change in the murine norovirus receptor and facilitates viral infection. Nat. Microbiol. 3, 1109–1114
32. Toelzer, C., Gupta, K., Yadav, S. K. N., Boruc, U., Davidson, A. D., Kavanagh Williamson, M., Shoemark, D. K., Garzoni, F., Staufner, O., Milligan, R., Capin, J., Mulholland, A. J., Spatz, J., Fitzgerald, D., Berger, L., et al. (2020) Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein. Cell. 179, 725–730
33. Goc, A., Niedzwiecki, A., and Rath, M. (2021) Polyunsaturated omega-3 fatty acids inhibit ACE2-controlled SARS-CoV-2 binding and cellular entry. Sci. Rep. 11, 2507
42. Raniga, K., and Liang, C. (2018) Interferons: reprogramming the metabolic network against viral infection. *Viruses*, 10, 36

43. Roulin, P. S., Murer, L. P., and Greber, U. F. (2018) A single point mutation in the rhinovirus 2B protein reduces the requirement for phosphatidylinositol 4-kinase class III beta in viral replication. *J. Virol.*, 92, e01622-18

44. Ishikawa-Sawada, T., Nagashima, S., Taniguchi, K., and Sasaki, J. (2018) Model of OSBP-mediated cholesterol supply to aichi virus RNA replication sites involving protein-protein interactions among viral proteins, ACBD5, OSBP, VAP-A/B, and SACL. *J. Virol.*, 92, e01552-17

45. Hsu, N. Y., Ilyin, O., Belov, G., Santana, M., Chen, Y. H., Takverian, R., Pui, C., van der Schaar, H., Kaushik-Rasu, N., Balla, T., Cameron, G. E., Ehrenfeld, E., van Kuppevelt, F. J., and Altan-Bonnet, N. (2010) Viral reorganization of the secretory pathway generates distinct organelles for RNA replication. *Cell*, 141, 799–811

46. Heaton, N. S., Perera, R., Berger, K. L., Khadka, S., Kubn, R. J., and Randall, G. (2010) Dengue virus nonstructural protein 5 redistributes fatty acid synthase to sites of viral replication and increases cellular fatty acid synthesis. *Proc. Natl. Acad. Sci. U. S. A.* 107, 17345–17350

47. Martin-Acebes, M. A., Blazquez, A. B., Jimenez de Oya, N., Escobal-Romero, E., and Saiz, J. C. (2011) West Nile virus replication requires fatty acid synthesis but is independent on phosphatidylcholine-4-phosphate lipids. *PLoS One*, 6, e24970

48. van Hemert, M. J., van den Worm, S. H., Knoops, K., Mommaas, A. M. G., Gorbalenya, A. E., and Snijder, E. J. (2008) SARS-coronavirus replication/transcription complexes are membrane-protected and need a host factor for activity in vitro. *PLoS Pathog.*, 4, e1000054

49. Knoops, K., Kikkert, M., Worm, S. H., Zevenhoven-Dobbe, J. C., van der Meer, Y., Koster, A. J., Mommaas, A. M., and Snijder, E. J. (2008) SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLoS Biol.*, 6, e226

50. Snijder, E. J., Limpens, R., de Wilde, A. H. de Jong, A. W. M., Zevenhoven-Dobbe, J. C., Maier, H. J., Faas, F., Koster, A. J., and Barcena, M. (2020) A unifying structural and functional model of the coronavirus replication organelle: tracking down RNA synthesis. *PLoS Biol.*, 18, e3000715

51. Maier, H. J., Hawes, P. C., Cottam, E. M., Mantell, J., Verkade, P., Monaghan, P., Wileman, T., and Britton, F. (2013) Infectious bronchiolitis virus generates spherolesomes from zipper-endoplasminic reticulum membranes. *mBio*, 4, e00801-13

52. Angelini, M. M., Akhlaghpour, M., Neuman, B. W., and Buchmeier, M. J. (2013) Severe acute respiratory syndrome coronavirus nonstructural proteins 3, 4, and 6 induce double-membrane vesicles. *mBio*, 4, e00524-13

53. Muller, C., Ho, M., Schwurcke, D., Neuman, B. W., Pleschka, S., and Ziebuhr, J. (2018) Inhibition of cytosolic phospholipase A2alpha impairs an early step of coronavirus replication in cell culture. *J. Virol.*, 92, e01463-17

54. Yan, B., Chu, H., Yang, D., Sze, K. H., Lai, P. M., Yuan, S., Shuai, H., Wang, Y., Kao, R. Y., Chan, J. F., and Yuen, K. Y. (2019) Characterization of the lipidomic profile of human coronavirus-infected cells implicated for lipid metabolism remodeling upon coronavirus infection. *Viruses*, 11, 73

55. Yuan, S., Chu, H., Chan, J. F., Ye, Z. W., Wen, L., Yan, B., Lai, P. M., Tso, K. M., Huang, J., Chen, D., Li, C., Zhao, X., Yang, D., Chu, M. C., Yip, C., et al. (2019) SREBP-dependent lipidomic reprogramming as a broad-spectrum antiviral target. *Nat. Commun.*, 10, 120

56. Wang, R., Simonet, C. R., Kulsumatrakul, J., Bouhaddou, M., Travisano, K. A., Hayashi, J. M., Carbon-Steeverner, J., Zengel, J. R., Richards, C. M., Fozouni, P., Oki, J., Rodriguez, L., Chehimi, M. H., Boland, R., and Runz, H. (2018) Identification of cholesterol-regulating genes by targeted RNAi screening. *Cell Metab.*, 18, 65–75

57. Gordon, D. E., Hiatt, J., Bouhaddou, M., Rezelj, V. V., Ulferts, S., Braberg, H., Jureka, A. S., Obernier, K., Guo, J. Z., Batta, J., Kaake, R. M., Weckstein, A. R., Owens, T. W., Gupta, M., Pourmal, S., et al. (2020) Comparative host-coronavirus interaction network reveals pan-viral disease mechanisms. *Scien., 370, eabc9403

58. Gordon, D. E., Jiang, G. M., Bouhaddou, M., Xu, J., Obernier, K., White, K. M., O'Meara, M. J., Rezelj, V. V., Guo, J. Z., Swaney, D. L., Tummino, T. A., Huttonhain, R., Kaake, R. M., Richards, A. L., and Tuttucuoglu, B., et al. (2020) A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*, 583, 459–468

59. Tummino, T. A., Rezelj, V. V., Fischer, B., Fischer, A., O'Meara, M. J., Monel, B., Vallely, T., Zhang, Z., Alon, A., O'Donnell, H. R., Lys, J., Schadt, H., White, K. M., Krogan, N. J., Urban, L., et al. (2021) Phospholipidosis is a shared mechanism underlying the in vitro antiviral activity of many repurposed drugs against SARS-CoV-2. *bioRxiv*. https://doi.org/10.1101/2021.03.25.436648

60. Hamock, B. D., Wang, W., Gilligan, M. M., and Panigrahi, D. (2009) Eicosanoids therapeutically modulate influenza virus disease 2019 (COVID-19). *J. Am. J. Pathol.*, 192, 1762–1778

61. Funk, C. D., and Ardkani, A. (2020) A novel strategy to mitigate the hyperinflammatory response to COVID-19 by targeting leukotrienes. *Front. Pharmacol.*, 11, 1214

62. Hoxha, M. (2020) What about COVID-19 and arachidonic acid pathway? *Eur. J. Clin. Pharmacol.*, 76, 1505–1511

63. Cares, K. M., Bradbury, J. A., Veeraraghavan, K. J., Lewis, J. M., Landenbach, R., Zeldin, D. C., and Germolec, D. R. (2015) Contrasting effects of cyclooxygenase-1 (COX-1) and COX-2 deficiency on the host

Lipids, virology and the immune response
response to influenza A viral infection. J. Immunol. 175, 6878–6884

75. Carey, M. A., Bradbury, J. A., Rebolloso, Y. D., Graves, J. P., Zeldin, D. C., and Gormolec, D. R. (2010) Pharmacologic inhibition of COX-1 and COX-2 in influenza A viral infection in mice. PLoS ONE 5, e1610.

76. Launder, S. N., Taylor, P. R., Clark, S. R., Evans, R. L., Hindley, J. P., Smart, K., Leach, H., Kiedl, E. J., Broadley, K. J., Jones, S. A., Wise, M. P., Godkin, A. J., O'Donnell, V., and Gallimore, A. M. (2011) Paracetamol reduces influenza-induced immunopathology in a mouse model of infection without compromising virus clearance or the generation of protective immunity. Thorax. 66, 974–977.

77. Li, C., Li, C., Zhang, A. J., Li, D. Y., Yuen, K. Y. (2008) Delayed antiviral plus immunomodulator treatment still reduces mortality in mice infected by high inoculum of influenza A/H5N1 virus. Proc. Natl. Acad. Sci. U. S. A. 105, 8091–8096.

78. Zhang, A. J., Zhu, H., Chen, Y., Li, C., Chu, H., Gozali, L., Lee, A. Y. C., To, K. W. K., Hung, I. F. N., and Yuen, K. Y. (2019) Prostaglandin E2-mediated impairment of innate immune response to A(H1N1)pdm09 infection in diet-induced obese mice could be restored by paracetamol. J. Infect. Dis. 219, 795–807.

79. Yambe, F., Jaworska, J., Verway, M., Tzelepis, F., Massoud, A., Panka, B. A., de Grooth, H. J., Spoelstra-de Man, A. M., Looney, M. P., Godkin, A. J., O’Reilly, E. W., Spann, K., Everard, M. L., and Phipps, S. (2018) PGD2/DP2 receptor activation promotes severe viral bronchiolitis by suppressing IFN-λ3 synthesis. Proc. Natl. Acad. Sci. U. S. A. 115, 9499–9504.

80. Hashimoto, K., Grahame, I. W., Spann, K., Everard, M. L., and Phipps, S. (2018) PDGFR/Δ2 receptor activation promotes severe viral bronchiolitis by suppressing IFN-λ3 synthesis. Proc. Natl. Acad. Sci. U. S. A. 115, 9499–9504.

81. Oka, T., Matsuka, T., Yama, C., Nonomura, K., Kitaoka, S., Sakata, D., Kita, Y., Tanizawa, K., Taguchi, Y., Chin, K., Mishima, M., Shimizu, T., and Narumiya, S. (2009) Prostaglandin F2α receptor signaling facilitates bleomycin-induced pulmonary fibrosis independently of transforming growth factor-beta. Nat. Med. 15, 1426–1430.

82. Kuhl, P. G., Bolds, J. M., Lloyd, J. E., Snapper, J. R., and FitzGerald, G. A. (1988) Thromboxane receptor-mediated bronchial and hemodynamic responses in ovine endotoxemia. Am. J. Physiol. 254, R310–R319.

83. Panka, B. A., de Grooth, H. J., Spoelstra-de Man, A. M., Looney, M. R., and Tzelepis, F. (2017) Prevention or treatment of severe bacterial pneumonia in a mouse model of infection with S. pneumoniae. J. Immunol. 199, 2191–2201.

84. Arnadottir, H., Pawelzik, S. C., Ohlund Wistbacka, U., Artiach, G., Hofmann, R., Reinholdsson, I., Braunschweig, E., Tornvall, P., Religa, D., and Back, M. (2020) Stimulating the resolution of inflammation through omega-3 polyunsaturated fatty acids in COVID-19: rationale for the COVID-omega-F trial. Front. Physiol. 11, 624657.
Metabolomic/lipidomic profiling of COVID-19 and individual response to tocilizumab. PLoS Pathog. 17, e1009243

Barberis, E., Timo, S., Amede, E., Vanella, V. V., Puricelli, C., Cappellano, G., Raineri, D., Cittone, M. G., Rizi, E., Pedrinelli, A. R., Vassia, V., Casartaro, F. G., Priora, S., Nericci, L., Galbiati, A., et al. (2020) Large-scale plasma analysis revealed new mechanisms and molecules associated with the host response to SARS-CoV-2. Int. J. Mol. Sci. 21, 8063

Sun, J. T., Chen, Z., Nie, P., Ge, H., Shen, L., Yang, F., Qu, X. L., Ying, X. Y., Zhou, Y., Wang, W., Zhang, M., and Pu, J. (2020) Lipid profile features and their associations with disease severity and mortality in patients with COVID-19. Front. Cardiovasc. Med. 7, 581487

Kimhsfer, T., Lodge, S., Whiley, L., Gray, N., Loo, R. L., Lawler, N. G., Nitschke, P., Bong, S. H., Morrison, D. L., Begum, S., Richards, T., Yeap, B. B., Smith, C., Smith, K. G. C., Holmes, E., et al. (2020) Integrative modeling of quantitative plasma lipoprotein, metabolic, and amino acid data reveals a multiorgan pathological signature of SARS-CoV-2 infection. J. Proteome Res. 19, 4442–4454

Lee, H. Y., Ahn, J., Park, J., Kyung Kang, C., Won, S. H., Wook Kim, D., Park, J. H., Chung, K. H., Joh, J. S., Bang, J. H., Hee Kang, C., Bum Pyun, W., Oh, M. D., Korean Society of Hypertension, and National Committee for Clinical Management of Emerging Infectious Diseases (2021) Beneficial effect of statins in COVID-19-related outcomes—brief report: a national population-based cohort study. Arterioscler. Thromb. Vasc. Biol. 41, e175–e182

Zhang, X. J., Qin, J. J., Cheng, X., Shen, L., Zhao, Y. C., Yuan, Y., Lei, F., Chen, M. M., Yang, H., Bai, L., Song, X., Lin, L., Xia, M., Zhou, F., Zhou, J., et al. (2020) In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metab. 32, 176–187.e4

Nie, X., Qian, L., Sun, R., Huang, B., Dong, X., Xiao, Q., Zhang, Q., Lu, T., Yue, L., Chen, S., Li, X., Sun, Y., Li, I., Xu, L., Li, Y., et al. (2021) Multi-organ proteomic landscape of COVID-19 autopsies. Cell. 184, 775–791.e4

Pelz, E. D., D’Alessandro, A., Moore, E. E., Chin, T., Silliman, C. G., Sauaia, A., Hansen, K. C., and Banerjee, A. (2015) Pathologic metabolism: an exploratory study of the plasma metabolome of critical injury. J. Trauma Acute Care Surg. 78, 742–751

Maile, M. D., Standiford, T. J., Engoren, M. G., Stringer, K. A., Jewell, E. S., Rajendiran, T. M., Soni, T., and Burant, C. F. (2018) Associations of the plasma lipidome with mortality in the acute respiratory distress syndrome: a longitudinal cohort study. Respir. Res. 19, 60

Feingold, K. R. (2021) The bidirectional link between HDL and COVID-19 infections. J. Lipid Res. 62, 100067

Acosta-Ampudia, Y., Monsalve, D. M., Rojas, M., Rodriguez, Y., Gallo, J. E., Salazar-Uribé, J. C., Santana, M. J., Cala, M. P., Zapata, W., Zapata, M. I., Manrique, R., Pardo-Oviedo, J. M., Camacho, B., Ramírez-Santana, C., Anaya, J. M., et al. (2021) COVID-19 covalescent plasma composition and immunological effects in severe patients. J. Autoimmun. 118, 102598

Xu, J., Zhou, M., Luo, P., Yin, Z., Wang, S., Liao, T., Yang, F., Wang, Z., Yang, D., Peng, Y., Geng, W., Li, Y., Zhang, H., and Yang, J. (2021) Plasma lipidomic profiling of patients recovered from COVID-19 with pulmonary sequelae 3 months after discharge. Clin. Infect. Dis. https://doi.org/10.1093/cid/ciaa147

Wu, Q., Zhou, L., Sun, X., Yan, Z., Hu, C., Wu, J., Xu, L., Li, X., Liu, H., Yin, P., Li, K., Zhao, J., Li, Y., Wang, X., Li, Y., et al. (2017) Altered lipid metabolism in recovered SARS patients twelve years after infection. Sci. Rep. 7, 9110

Shen, B., Yi, X., Sun, Y., Bi, X., Du, J., Zhang, C., Quan, S., Zhang, F., Sun, R., Qian, L., Ge, W., Liu, W., Liang, S., Chen, H., Zhang, Y., et al. (2020) Proteomic and metabolic characterization of COVID-19 patient sera. Cell. 182, 59–72.e15

Song, J. W., Lam, S. M., Fan, X., Cao, W. J., Wang, S. Y., Tian, H., Chua, G. H., Zhang, C., Meng, F. P., Xu, Z., Fu, J. L., Huang, J., Xia, P., Yang, Z., Zhang, S., et al. (2020) Omics-driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis. Cell Metab. 32, 188–202.e5

Winkler, M. S., Marz, K. B., Nierhaus, A., Daum, G., Schwedhelm, E., Klüge, S., and Graier, M. H. (2019) Loss of sphingosine 1-phosphate (SIP) in septic shock is predominantly caused by decreased levels of high-density lipoproteins (HDL). J. Intensive Care. 7, 23

Walsh, K. B., Teijaro, J. R., Wilker, P. R., Jatzek, A., Freemgen, D. M., Das, S. C., Watanabe, T., Hatta, M., Shinya, K., Suresh, M., Kawaoka, Y., Rosen, H., and Oldstone, M. B. (2011) Suppression of cytokine storm with a sphingosine analog provides protection against pathogenic influenza virus. Proc. Natl. Acad. Sci. U. S. A. 108, 12908–12923

Teijaro, J. R., Walsh, K. B., Cahalan, S., Freemgen, D. M., Roberts, E., Scott, F., Martinborough, E., Peachi, R., Oldstone, M. B., and Rosen, H. (2011) Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. Cell. 146, 980–991

Teijaro, J. R., Walsh, K. B., Rice, S., Rosen, H., and Oldstone, M. B. (2014) Mapping the innate signaling cascade essential for cytokine storm during influenza virus infection. Proc. Natl. Acad. Sci. U. S. A. 111, 3799–3804

Zhang, J., Zhu, M., Jiang, H., Shen, S., Su, X., and Shi, Y. (2019) Combination of sphingosine-1-phosphate receptor 1 (SIPR1) agonist and antiviral drug: a potential therapy against pathogenic influenza virus. Sci. Rep. 9, 5272

Seo, Y., Blake, C., Alexander, S., and Hahm, B. (2010) Sphingosine 1-phosphate-metabolizing enzymes control influenza virus propagation and viral cytopathogenicity. J. Virol. 84, 8124–8131

Seo, Y. J., Pritzl, C. J., Vijayan, M., Bomb, K., McClain, M. E., Alexander, S., and Hahm, B. (2013) Sphingosine kinase 1 serves as a pro-viral factor by regulating viral RNA synthesis and nuclear export of viral ribonucleoprotein complex upon influenza virus infection. PLoS One 8, e75005

Xia, C., Seo, Y. J., Studdifield, C. J., Vijayan, M., Wolf, J. J., and Hahm, B. (2018) Transient inhibition of sphingosine kinases confers protection to influenza A virus infected mice. Antiviral Res. 158, 171–177

Vijayan, M., Xia, C., Song, Y. E., Ngo, H., Studdifield, C. J., Drews, K., Fox, T. E., Johnson, M. C., Hiscott, J., Kester, M., Alexander, S., and Hahm, B. (2017) Sphingosine 1-phosphate lyase enhances the activation of IKKepsilon to promote type I IFN-mediated innate immune responses to influenza A virus infection. J. Immunol. 199, 677–687

Yan, Q., Li, F., Ye, X., Huang, X., Peng, B., Ji, T., Chen, Z., Li, F., Zhang, Y., Luo, K., Chen, F., Mo, X., Wang, J., Feng, L., Hu, F., et al. (2021) Longitudinal peripheral blood transcriptional analysis reveals molecular signatures of disease progression in COVID-19 patients. J. Immunol. 206, 2146–2159

Schwarz, B., Sharma, L., Roberts, L., Peng, X., Bermejo, S., Leighton, I., Casanova-Massana, A., Minasyan, M., Farhadian, S., Ko, A. I., Yale, I. T., Dela Cruz, C. S., and Bosco, C. M. (2021) Cutting edge: severe SARS-CoV-2 infection in humans is defined by a shift in the serum lipodrome, resulting in dysregulation of eicosanoid immune mediators. J. Immunol. 206, 329–334

Snider, M. J., You, J. K., Wang, X., Snider, A. J., Hallmark, B., Seeds, M. C., Sergeant, S., Johnstone, L., Wang, Q., Sprisler, R., Zhang, H. H., Luberto, C., Kew, R. R., Hannum, Y. A., McColl, C. E., et al. (2021) Group IIa secreted phospholipase A2 plays a central role in the pathobiology of COVID-19. J. Clin. Invest. 131, e149236