Elevation in sphingolipid upon SARS-CoV-2 infection: possible implications for COVID-19 pathology

Einat B Vitner, Roy Avraham, Boaz Politi, Sharon Melamed, Tomer Israely

Understanding pathways that might impact coronavirus disease 2019 (COVID-19) manifestations and disease outcomes is necessary for better disease management and for therapeutic development. Here, we analyzed alterations in sphingolipid (SL) levels upon infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection induced elevation of SL levels in both cells and sera of infected mice. A significant increase in glycosphingolipid levels was induced early post SARS-CoV-2 infection, which was essential for viral replication. This elevation could be reversed by treatment with glucosylceramide synthase inhibitors. Levels of sphinganine, sphingosine, GA1, and GM3 were significantly increased in both cells and the murine model upon SARS-CoV-2 infection. The potential involvement of SLs in COVID-19 pathology is discussed.

DOI 10.26508/lsa.202101168 | Received 23 July 2021 | Revised 25 October 2021 | Accepted 26 October 2021 | Published online 11 November 2021

Introduction

In December 2019, the novel coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified as the causative agent of a cluster of acute atypical pneumonia cases in the city of Wuhan, China (Zhou et al., 2020). In February 2020, the World Health Organization named the disease COVID-19 (Yang & Wang, 2020).

COVID-19 primarily manifests as a respiratory tract infection causing hypoxic respiratory failure. However, there is an enormous amount of data demonstrating that it may involve multiple organ systems, including the nervous, cardiovascular, respiratory, gastrointestinal, renal, hematopoietic, and immune systems (Erdinc et al., 2021). Understanding pathological pathways involved in COVID-19 manifestations might reveal new approaches for therapeutic strategies and disease management.

Sphingolipids (SLs) are a major class of eukaryotic cell membrane constituents. In addition to playing a structural role, some SLs are bioactive and control vital biological functions by regulating signal transduction pathways involved in several processes. Some bioactive SLs are implicated in pathological processes, including inflammation-associated illnesses such as atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, type II diabetes, obesity, cancer, and neurological and neurodegenerative diseases (Ogretmen, 2018; D’Angelo et al., 2019; Hussain et al., 2019; Gomez-Larrauri et al., 2020). Furthermore, SLs play an important role in the control of virus replication and the innate immune response (Schneider-Schaulies & Schneider-Schaulies, 2013; Schneider-Schaulies & Schneider-Schaulies, 2015; Bezgovsek et al, 2018; Yager & Konan, 2019; Melamed et al, 2020; Vitner, 2020).

Bioactive SLs are regulated by various enzymes and fluxes of different metabolites, with ~40 enzymes involved in their metabolism in mammals (Hannun & Obeid, 2018) (see Fig S1 for the SL synthesis pathway). Glycosphingolipids (GSLs) are a heterogeneous group of membrane lipids formed by a Cer backbone covalently linked to a glycan moiety. Glucosphingolipids depend initially on the enzyme glucosylceramide (GlcCer) synthase (GCS), which attaches glucose as the first residue to the C1 hydroxyl position (D’Angelo et al., 2013).

Recent studies suggested a role of sphingolipids in modulating SARS-CoV-2 infection (Carpinteiro et al., 2020; Törnquist et al., 2021). In addition, we have recently shown that the synthesis of GSLs is necessary to support SARS-CoV-2 replication in vitro, suggesting alterations in SL levels upon SARS-CoV-2 infection (Vitner et al., 2021).

In this study, we show that SARS-CoV-2 induces an increase in the levels of SLs in vitro and in vivo and discuss the possible implications of such alterations.

Results

SARS-CoV-2 infection induces an increase in SL levels early upon infection

Previously reported data suggest that inhibiting GCS interrupts early stages in the replication cycle of SARS-CoV-2 (Vitner et al., 2021). Thus, SL levels were examined in Vero E6 cells at an early stage upon infection with SARS-CoV-2. At 3 hours post infection (hpi) with SARS-Cov-2, a significant elevation in 3-ketosphinganine (3KSa) (d16:0, d18:0, d18:1, and d20:0), sphinganine (Sa), sphingosine (So), and sphinganine-1-phosphate (d18:0-P and Sa1P) levels was detected (Fig 1).
The alteration of SL levels was also reflected by an elevation in the levels of many other downstream SLs; DH Cer and Cer levels were significantly elevated in SARS-CoV-2-infected cells (Fig 2). In addition, SARS-CoV-2 induced a significant elevation in GSL levels and, to a lesser extent, in DHSM, SM and C1P levels (Fig 2). Hexosylceramide (HexCer, β-galactosylceramide [GalCer] and β-GlCer) levels were mostly elevated, as well as the levels of lactosylceramides (LacCers) (Fig 2). The elevation was not specific to certain fatty acid chain lengths and seemed to re-

et al, 2007). GZ-346 signi-
treatment of adult patients with Gaucher disease type 1 (GD1) (Zhao (Genz-123346), termed hereafter GZ-346. GZ-346 is an analog of the hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-l-tartaric acid salt β-

- galactosylceramide [GalCer] and β-GlcCer) levels were

cant differences in the levels of Cer, LacCer, GA1, GA2, and GM3 upon SARS-CoV-2 infection (Fig 2). In addition, similar to the elevation observed in infected cells (Fig 3), the levels of GA1 (C:16), GA2 (C:16:0 and C:24:0), and GM3 (C:16:0) were significantly increased in the sera of SARS-CoV-2-infected mice (Figs 6 and S2B). The levels of LacCer were unaltered (Fig 6).

In addition to those for Sa, alterations in downstream SL levels were also detected: DH Cer (C:16:0 and C:20:0), Cer (C:6:0 and C:24:0), HexCer (C:14:0, C:16:0, C:18:1, C:22:0, and C:23:0), DHSM (C:16:0, C:18:0, and C:18:1), SM (C:10:0, C:12:0, C:16:0, C:18:0, C:18:1, C:20:1, and C:20:0), and C1P (C:12:0, C:14:0, C:16:0, C:18:0, C:18:1, and C:20:0) levels were elevated in the sera of SARS-CoV-2-infected mice (Figs 6 and S2B). The levels of LacCer were unaltered (Fig 6).

In addition, similar to the elevation observed in infected cells (Fig 3), the levels of GA1 (C:16), GA2 (C:16:0 and C:24:0), and GM3 (C:16:0) were significantly increased in the sera of SARS-CoV-2-infected mice (Figs 7 and S2B).

Discussion

SARS-CoV-2 infection induces elevation of SLs not only in cells but also in vivo. Levels of Sa, So, GA1, and GM3 were significantly increased in both cells and the murine model upon SARS-CoV-2 infection. The mechanism by which SARS-CoV-2 induces elevation in SLs needs to be elucidated. It was recently shown that pseudoviral SARS-CoV-2 induces acid sphingomyelinase activity, which affects the levels of ceramide (Carpinteiro et al, 2020). However, our data, demonstrating elevation of several SL species, together with previous data showing that inhibition of GCS is important to viral replication, suggest that the activity of an early enzyme in the SL synthesis pathway is elevated. These data are consistent with previous studies demonstrating the involvement of fatty acid synthase (FASN) in the replication of many viruses (Li et al, 2004;
Kapadia & Chisari, 2005; Machesky et al, 2008; Yang et al, 2008; Diamond et al, 2010; Heaton et al, 2010; Perera et al, 2012; Huang et al, 2013; Tongluan et al, 2017; Chotiwan et al, 2018). Although the focus of this study is SLs, it is reasonable that other lipid levels are also altered by SARS-CoV-2.

SARS-CoV-2 significantly increased the levels of Sa and So in the serum. Alterations in So levels in symptomatic COVID-19 patients were recently described (Janneh et al, 2021). However, whereas symptomatic COVID-19 patients exhibited a robust decrease in their serum sphingosine levels, the mice exhibited the opposite effect. This difference might be a result of the time point of serum detection, and more studies should be conducted to answer this question.

Increases in the serum levels of Sa and So have implications in cardiovascular dysfunction; fumonisin B1 (FB1), a mycotoxin, has been shown to lead to altered SL biosynthesis and dose-dependent increases in serum and tissue Sa and So concentrations (Riley et al, 1993). In pigs, ingestion of FB1 has been shown to affect the cardiovascular system, causing cardiovascular dysfunction (Smith et al, 1996; Smith et al, 1999; Constable et al, 2000). Moreover, SL metabolism has been suggested to be involved in the pathophysiology of Kawasaki disease (KD), an acute systemic vasculitis (Konno et al, 2015). Inhibition of sphingolipid de novo synthesis has been shown to improve atherogenesis signs (Park et al, 2004; Hojjati et al, 2005; Glaros et al, 2007; Hornemann & Worgall, 2013; Borodzicz et al, 2015). An association between COVID-19 cardiovascular disease and KD has been reported (Viner & Whittaker, 2020). Preexisting cardiovascular disease seems to be linked with worse outcomes and increased risk of death in patients with COVID-19, whereas COVID-19 itself can also induce myocardial injury, arrhythmia, acute coronary syndrome and venous thromboembolism (Nishiga et al, 2020). Whether elevation of SL levels contributes to cardiovascular manifestations observed in SARS-CoV-2 has not been examined.

The elevation of gangliosides in response to SARS-CoV-2 is intriguing. Gangliosides are ubiquitously found in tissues and body fluids and are most abundantly expressed in the nervous system (Sipione et al, 2020). Anti-ganglioside antibodies (AGAs) are associated with an autoimmune condition in which the host’s immune system attacks the gangliosides of neurons (Willison et al, 2016). There is growing evidence indicating that neurological manifestations occur in patients with COVID-19 (Sharifan-Dorche et al, 2020; Andalib et al, 2021; Shehata et al, 2021). Our data showing increased levels of gangliosides in the sera of SARS-CoV-2–infected mice can provide a distinct potential mechanism by which elevated levels of host GSLs upon viral infection may trigger AGA generation.

GM1 is the most common AGA found in patients with GBS, whereas GO1b is associated with MFS. Aside from one case report, a review of available articles yields no reported cases of COVID-19-related GBS or MFS that included positive tests for GM1 or GO1b (Dufour et al, 2021). Our data indicate no elevation in GM1 levels in cells or sera upon SARS-CoV-2 infection, but GA1, GA2, and mostly

![Figure 2. SARS-CoV-2 infection induces elevation of GSL levels in vitro.](https://doi.org/10.26508/lsa.202101168)
Sphingolipids and SARS-CoV-2

Vitner et al.

Using GraphPad Prism software version 8.4.3. Complete dataset in Table S2. GM3 levels were elevated (Figs 3 and 7). Interestingly, GM3 is a major ganglioside in the lungs (Iwamori et al, 1984) that is primarily infected by SARS-CoV-2. However, it is important to note that our study was performed in a transgenic mouse model and in Vero E6 cells. The specific models that were examined might affect the GSL profile that is being altered. Thus, a comprehensive unlimited analysis of gangliosides and anti-GSL antibodies in patients with COVID-19 might reveal novel target(s).

Interestingly, the SL elevation observed in the asymptomatic mice was similar to that observed in symptomatic mice. Thus, the elevation of SLs does not seem to be involved directly in pathogenesis and disease severity. However, if elevated SL indeed contributes to long-term manifestations, our data suggest that SL-related complications might also be present in asymptomatic individuals upon infection with SARS-CoV-2. This can suggest an explanation for signs, such as neurological and cardiovascular signs, with unknown etiology.

In addition to their potential role in pathology, SLs were found to be significantly useful markers of disease prediction, diagnosis, prognosis and treatment monitoring (Matanes et al, 2019). SLs have been linked to the pathophysiology of many diseases in the human body, including cardiovascular diseases, cancer, metabolic disorders, dementia, and mental diseases (Matanes et al, 2019) and recently also in COVID-19 (Janneh et al, 2021). Our data, showing elevation in SL levels in all infected mice, suggest the possible use of SLs as diagnostic biomarkers for viral diseases. This possibility should be further evaluated in patients rather than in mice.

Our data support the need for further research on the role of SLs in SARS-CoV-2 infection. First, SL quantification in patient serum will delineate whether the enrichment observed in the transgenic mouse model recapitulates the enrichment in humans. In addition, quantification of SLs upon other viral infections is needed to determine whether alterations in SL levels are common to many viruses. Next, studies exploring the role of SLs in cardiovascular and neurological complications in COVID-19 patients might open new therapeutic targets. The availability of FDA-approved drugs with the capacity to restore the elevation of serum GSL levels may reveal new strategies to prevent COVID-19 clinical complications.

Materials and Methods

Cell sample preparation

Vero E6 (ATCC CRL-1586) cells were obtained from the American Type Culture Collection. Cells were grown in DMEM supplemented with 10% FBS, MEM nonessential amino acids (NEAAs), 2 mM L-glutamine, 100 units/ml penicillin, 0.1 mg/ml streptomycin, and 12.5 units/ml nystatin (P/S/N) (Biological Industries). Cells were cultured at 37°C in a 5% CO₂ and 95% air atmosphere.

Vero E6 cells were seeded at a density of 1 × 10⁶ cells per 60 mm plate. After incubating overnight, cells were treated in four replicates with 10 μM GZ-346. The cells were infected 1 h later with SARS-CoV-2 (MOI: 5). At 3 hpi, the cells were washed three times in cold PBS and collected with a rubber policeman.

GZ-346 ((1R,2R)-nonanoic acid [2-(2'-9-dihydro-benzo [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-l-tartaric acid salt) was obtained from Sanoﬁ. The compound was stored as a 5 mM stock solution in PBS at −20°C until use.

Animal experiment

Treatment of animals was in accordance with regulations outlined in the U.S. Department of Agriculture (USDA) Animal Welfare Act and the conditions specified in the Guide for Care and Use of Laboratory Animals (National Institutes of Health, 2011). Animal studies were approved by the local ethics committee on animal experiments (protocol number M-51-20). Male and female K18-hACE2 transgenic (B6.CgTg(K18ACE2)2Prlm/J) (HEMI) mice (Jackson Laboratories) were maintained at 20–22°C and a relative humidity of 50 ± 10% on a 12-h light/dark cycle, fed commercial rodent chow (Koffolk Inc.), and provided with tap water ad libitum. Animals were 6- to 8-wk old. All animal experiments involving SARS-CoV-2 were conducted in a BSL3 facility. Infection experiments were carried out using the SARS-CoV-2 isolate Human 2019-nCoV ex China strain BavPat1/2020, which was kindly provided by Prof. Christian Drosten (Charité) through the European Virus Archive—Global (EVAg Ref-SKU: 026V-03883). The original viral isolate was amplified by five passages, quantified by a plaque titration assay in Vero E6 cells, and stored at...
−80°C until use. The viral stock DNA sequence and coding capacity were confirmed as recently reported (Finkel et al., 2021). The SARS-CoV-2 BavPat1/2020 virus (20 pfu) diluted in PBS supplemented with 2% FBS (Biological Industries) was used to infect animals by intranasal instillation (20 μl) of anesthetized mice. Control groups were administered PBS. Serum samples were collected at day 5 post infection from SARS-CoV-2–infected and control mice. All sera were heat-inactivated (HI) (at 56°C for 30 min).

**Sphingolipid quantification**

**Sample preparation**

Each cell pellet and each 50 μl serum sample were suspended in 100 μl of methanol/chloroform (1:1), and the samples were sent to The Metabolomics Innovation Centre (TMIC) for analysis. Each sample was mixed with 100 μl of a mixture of 5 deuterium-labeled sphingolipids as internal standards and 300 μl of methanol/chloroform (3:1) containing BHT as an antioxidant. The mixture was vortexed for 2 min at 1,000 g and then ultrasonicated in an ice-water bath for 5 min before centrifugal clarification for 10 min at 21,000g. The clarified supernatant was collected for LC-MRM/MS, and the protein pellet was used to perform protein quantitation using a standardized Bradford procedure.

**Calibration solutions and LC–MS**

A mixed standard–substrate stock solution of targeted sphingolipids was prepared at a concentration of 40 μM for each compound in methanol-chloroform (3:1) containing BHT as an antioxidant. The mixture was vortexed for 2 min at 1,000g and then ultrasonicated in an ice-water bath for 5 min before centrifugal clarification for 10 min at 21,000g. The clarified supernatant was collected for LC-MRM/MS, and the protein pellet was used to perform protein quantitation using a standardized Bradford procedure.
Waters Acquity UPLC system coupled to a 4000 QTRAP mass spectrometer, which was operated in multiple-reaction monitoring (MRM) mode with positive ion detection for sphingolipids and negative ion detection for sphingolipid phosphates. The mobile phase was 0.01% formic acid in water and acetonitrile-isopropanol (2:1) for binary-solvent gradient elution (25–100% organic solvent in 12.5 min), followed by a 3-min column cleanup and 4-min column equilibration at 400 μl/min and 55°C. The ion transitions for MRM detection of each sphingolipid were optimized by direction infusion of an individual standard solution to produce two ion transitions per compound. The UPLC-MRM/MS data files were recorded using Sciex Analyst 1.6 software and were processed using Sciex MultiQuant 2.0 software. Linear regression calibration curves of individual sphingolipids were constructed with internal-standard calibration, and the concentrations of sphingolipids detected in each sample were calculated from the calibration curves with the measured analyte-to-internal standard peak area ratios.

Gangliosides were detected on an LTQ-Orbitrap Velos Pro with high mass resolution detection (FWHM 60,000 at m/z 400) in a mass range of m/z 300–2,000 and in positive ion mode. Gangliosides were assigned based on comparison of the measured accurate masses of gangliosides to their theoretically calculated masses within an allowable mass error of 3 ppm and with the aid of standard substances of the gangliosides GM1, GM2, and GM3. The ion chromatograms of detected gangliosides were extracted using their accurate masses within a mass window of 3 ppm, and the peak areas were used for relative quantitation. Peak area was normalized to milligrams of protein.

Statistical analysis

Statistical analyses were performed with a two-tailed unpaired t test or one-way ANOVA followed by Tukey’s multiple comparison test, as indicated in the figure legends. P-values are indicated by asterisks in the figures, as follows: *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001. Differences with a P-value of 0.05 or less were considered significant. The exact value of n is indicated in the figure legends. Data for all measurements are expressed as the means ± SEMs. Analyses were performed using GraphPad Prism software version 8.4.3.

Data Availability

This manuscript does not have large-scale data sets to deposit to the public databases.

Supplementary Information

Supplementary information is available at https://doi.org/10.26508/lsa.202101168.

ceramide-1-phosphate. Data are means ± SEMs. Statistical analysis was performed using a two-tailed unpaired t test. P-values are indicated by asterisks, as follows: *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001. Differences with a P-value of 0.05 or less were considered significant. Graphs were generated using GraphPad Prism software version 8.4.3. Complete dataset in Table S3.
Acknowledgements

We thank Jun Han from TMIC for SL quantification. We thank Pablo Sardi (Sanofi) for providing GZ-346. We thank Shai Weiss for Safety advice.

Author Contributions

EB Vitner: conceptualization, formal analysis, supervision, funding acquisition, and writing—original draft, review, and editing.

R Avraham: data curation and writing—review and editing.

B Politi: data curation.

S Melamed: data curation.

T Israely: conceptualization and writing—review and editing.

Conflict of Interest Statement

Data are in United States Provisional Patent Application No. 63/014,386 “Glucosylceramide synthase inhibitors for prevention and treatment of viral diseases.”

References

Alessenko AV, Albi E (2020) Exploring sphingolipid implications in neurodegeneration. Front Neurol 11: 437. doi:10.3389/fneur.2020.00437

Andalib S, Biller J, Di Napoli M, Moghimi N, McCullough LD, Rubinos CA, O’Hana Noblezza C, Azarpazhooh MR, Catanese L, Elicer I, et al (2021) Peripheral nervous system manifestations associated with COVID-19. Curr Neurol Neurosci Rep 21: 9. doi:10.1007/s11910-021-01102-5

Bezgovsek J, Gubins E, Friedrich SK, Lang KS, Duhan V (2018) Sphingolipids in early viral replication and innate immune activation. Biol Chem 399: 1115–1123. doi:10.1515/hsc-2018-0181

Bordzicz S, Czarzasta K, Kuch M, Cudnoch-Jedrzejewska A (2015) Sphingolipids in cardiovascular diseases and metabolic disorders. Lipids Health Dis 14: 55. doi:10.1186/s12944-015-0053-y

Carpinteiro A, Edwards MJ, Hoffmann M, Kochs G, Gripp B, Weigang S, Adams C, Carpineiro E, Gubins A, Keitsch S, et al (2020) Pharmacological inhibition of acid sphingomyelinase prevents uptake of SARS-CoV-2 by epithelial cells. Cell Rep Med 1: 100142. doi:10.1016/j.xcrm.2020.100142

Chotiwon N, Andre BG, Sanchez-Vargas I, Islam MN, Grabowski JM, Hopf-Jannasch A, Gough E, Nakayasu E, Blair CD, Belisle JT, et al (2018) Dynamic remodeling of lipids coincides with dengue virus replication in the midgut of Aedes aegypti mosquitoes. PLoS Pathog 14: e1006853. doi:10.1371/journal.ppat.1006853

Constable PD, Smith GW, Rottinghaus GE, Haschek WM (2000) Ingestion of fumonisin B1-containing culture material decreases cardiac contractility and mechanical efficiency in swine. Toxicol Appl Pharmacol 162: 151–160. doi:10.1006/tapp.1999.8831

D’Angelo G, Capasso S, Sticco L, Russo D (2013) Glycosphingolipids: Synthesis and functions. FEBS J 280: 6338–6353. doi:10.1111/febs.12559

D’Angelo G, Clarke CJ, Silva LC (2019) Meeting report: The 2019 FEBS special meeting on sphingolipid biology: Sphingolipids in physiology and pathology. J Cell Sci 132: jcs235705. doi:10.1242/jcs.235705

Diamond DL, Syder AJ, Jacobs JM, Sorensen CM, Walters KA, Prokić S, McDermott JE, Gritsenko MA, Zhang Q, Zhao R, et al (2010) Temporal proteome and lipidome profiles reveal hepatitis C virus-associated reprogramming of hepatocellular metabolism and bioenergetics. PLoS Pathog 6: e1000719. doi:10.1371/journal.ppat.1000719

Dufour C, To T-K, Liu A (2021) GM1 ganglioside antibody and COVID-19 related Guillain Barre Syndrome: A case report, systemic review and implication for vaccine development. Brain Behav Immun Health 12: 100203. doi:10.1016/j.bbih.2021.100203

Erdinc B, Sahni S, Gottlieb V (2021) Hematological manifestations and complications of COVID-19. Adv Clin Exp Med 30: 101–107. doi:10.7219/acem/130604

Finkel Y, Mizrahi O, Nachshon A, Weingarten-Gabbay S, Morgenstern D, Finkel Y, Mizrahi O, Nachshon A, Weingarten-Gabbay S, Morgenstern D, Lebowitz BD, et al (2021) Sphingolipid metabolism in swine. FEBS J 280: 6307–6322. doi:10.1111/febs.14362

Glan G, Clark C, Co T-K, Liu A (2021) GM1 ganglioside antibody and COVID-19 related Guillain Barre Syndrome: A case report, systemic review and implication for vaccine development. Brain Behav Immun Health 12: 100203. doi:10.1016/j.bbih.2021.100203

Gomez-Larrauri A, Presa N, Dominguez-Herrera A, Ouro A, Trueba M, Gomez-Muñoz A (2020) Role of bioactive sphingolipids in physiology and pathology. Essays Biochem 64: 579–589. doi:10.1042/EBC20190001

Hannun YA, Obeid LM (2018) Sphingolipids and their metabolism in physiology and disease. Nat Rev Mol Cell Biol 19: 175–191. doi:10.1038/nrm.2017.107

Heaton NS, Perera R, Berger KL, Khadka S, LaCount DJ, Kuhn RJ, Randall G, Diamond DL, Syder AJ, Jacobs JM, Sorensen CM, Walters KA, Prokić S, McDermott JE, Gritsenko MA, Zhang Q, Zhao R, et al (2010) Temporal proteome and lipidome profiles reveal hepatitis C virus-associated reprogramming of hepatocellular metabolism and bioenergetics. PLoS Pathog 6: e1000719. doi:10.1371/journal.ppat.1000719

Hojjati MR, Li Z, Huan C, Ooi E, Lu S, Jiang XC (2005) Effect of myriocin on plasma sphingolipid metabolism and atherosclerosis in apoE-deficient mice. J Biol Chem 280: 10284–10289. doi:10.1074/jbc.M412348200

Figure 7. SARS-CoV-2 infection induces elevation in ganglioside levels in murine serum.

K18-HACE2 transgenic mice were infected with SARS-CoV-2 (20 pfu, intranasally inoculated, n = 5) or uninfected (control, n = 5). Ganglioside levels in serum samples obtained at day 5 post-infection were analyzed by LC–MS. The LC–MS peak area was divided by milligrams of protein in the sample for calibration. GA1, asialo GM1; GA2, asialo GM2. Statistical analysis was performed using a two-tailed unpaired t test. P-values are indicated by asterisks, as follows: ** P < 0.01. Differences with a P-value of 0.05 or less were considered significant. Graphs were generated using GraphPad Prism software version 8.4.3. Complete dataset in Table S2.
Sphingolipids and SARS-CoV-2
Vitner et al.

https://doi.org/10.26508/lsa.202101168
vol 5 | no 1 | e202101168

8 of 9
Zhao H, Przybylska M, Wu IH, Zhang J, Siegel C, Komarnitsky S, Yew NS, Cheng SH (2007) Inhibiting glycosphingolipid synthesis improves glycemic control and insulin sensitivity in animal models of type 2 diabetes. Diabetes 56: 1210–1218. doi:10.2337/db06-0719

Zheng W, Kollmeyer J, Symolon H, Momin A, Munter E, Wang E, Kelly S, Allegood JC, Liu Y, Peng Q, et al (2006) Ceramides and other bioactive sphingolipid backbones in health and disease: Lipidomic analysis, metabolism and roles in membrane structure, dynamics, signaling and autophagy. Biochim Biophys Acta 1758: 1864–1884. doi:10.1016/j.bbamem.2006.08.009

Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579: 270–273. doi:10.1038/s41586-020-2012-7

License: This article is available under a Creative Commons License (Attribution 4.0 International, as described at https://creativecommons.org/licenses/by/4.0/).