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Review

Host sphingolipids: Perspective immune adjuvant for controlling SARS-CoV-2 infection for managing COVID-19 disease

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ABSTRACT

Sphingolipids are potent bioactive agents involved in the pathogenesis of various respiratory bacterial infections. To date, several sphingolipid derivatives are known, but S1P (Sphingosine-1-phosphate) and Ceramide are the best-studied sphingolipid derivatives in the context of human diseases. These are membrane-bound lipids that influence host-pathogen interactions. Based on these features, we believe that sphingolipids might control SARS-CoV-2 infection in the host. SARS-CoV-2 utilizes the ACE-II receptor (Angiotensin-converting enzyme II receptor) on epithelial cells for its entry and replication. Activation of the ACE-II receptor is indirectly associated with the activation of S1P Receptor 1 signaling which is associated with IL-6 driven fibrosis. This is expected to promote pathological responses during SARS-CoV-2 infection in COVID-19 cases. Given this, mitigating S1P signaling by application of either S1P Lyase (SPL) or S1P analog (Fingolimod / FTY720) seems to be potential approach for controlling these pathological outcomes. However, due to the immunosuppressive nature of FTY720, it can modulate hyper-inflammatory responses and only provide symptomatic relief, which may not be sufficient for controlling the novel COVID-19 infection. Since Th1 effector immune responses are essential for the clearance of infection, we believe that other sphingolipid derivatives like Ceramide-1 Phosphate with antiviral potential and adjuvant immune potential can potentially control SARS-CoV-2 infection in the host by its ability in enhancing autophagy and antigen presentation by DC to promote T cell response which can be helpful in controlling SARS-CoV-2 infection in novel COVID-19 patients.

1. Introduction

Sphingolipids are bioactive agents and amphipathic molecules and are fundamentally involved in the pathogenesis of several respiratory diseases ranging from asthma, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and pulmonary infections [1] in the host. Sphingolipids are interconvertible, and their metabolism is strictly regulated. This enables them to both integrate and regulate a plethora of cellular functions. Sphingosine-1-phosphate (S1P) and Ceramide are two most commonly studied sphingolipid metabolites and their rheostat are important for the progression of various pathologies, which are manifested by inflammatory cascade. While Ceramide and free sphingosine induce cell death, S1P and Ceramide-1-phosphate (C1P) promote homeostasis [2]. Therefore, a fine balance in the level of Ceramide and other sphingolipid metabolites particularly S1P is critical for cellular homeostasis as well as for immunity against infections.

Sphingolipids are amphipathic bio-molecules formally derived from phosphorylation of D-sphingosine. These are produced mainly by two pathways: de novo sphingolipid biosynthesis or by breakdown of ceramide. In de novo biosynthesis, the first step is the condensation of L-serine and palmitoyl-CoA through the action of serine palmitoyl-transferase to form 3-ketodihydrosphingosine, which is then reduced to dihydro-sphingosine [3]. Acylation of dihydro-sphingosine produces ceramide, which can form sphingomyelin after conjugating with phosphocholine. However, sphingosine cannot be synthesized by the de novo pathway and is generated instead via the deacylation of ceramide catalyzed by ceramidase by salvage pathway [4]. Phosphorylation of sphingosine and ceramide by sphingosine kinases and ceramide kinase

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viral nuclear particle. Similarly, it was demonstrated that SK1 is critical for the perturbation in the biosynthesis or depletion of host sphingomyelin and viral maturation, budding, propagation [17]. Interestingly SK1/S1P is associated with the inhibition of ERK and NF-κB signaling pathways which regulate the cell survival pathway upon infection. SARS-CoV2 interacts with angiotensin-converting enzyme 2 (ACE2) receptors on alveolar epithelial cells for its attachment and entry [21,22]. Since ACE2 / Angiotensin-II receptors and SIP receptor 1 (SIPR1) signaling is known to cooperate to promote IL-6 induced myopathy and fibrosis [23] in a mouse model cardiac hypertrophy. On the basis of this report, it is possible that a crosstalk of these receptors may contribute to fibrosis in COVID-19 patients as well. Interestingly, S1PR1 signaling is associated with Th1 / Th2 /17 responses [24,25] in context dependent manner. Apart from this, SIPR1 signaling promotes hypoxia, asthmatic reactions [26] and anti-inflammatory response [27,28] in cancer patients. On account of this and increased expression of SK1 and SIP turnover in the virus-infected host, it is logical to presume that increased SIP signaling is likely to promote SARS-CoV-2 infection / replication in COVID-19 patients and warrant investigation.

SIP is a potent "find me" signal inducing a sterile inflammatory response, and may polarize M1 effector macrophages and CD4 + T cells toward M2 (foamy macrophages), and regulatory T cells in the infected organs (Ref). Moreover, SIPR1 signaling is known to activate Ras, MAPK, P38/AKT, and mTOR pathways, which drive substantial Th2 /17 responses [23] hypoxia, allergic manifestations [26] and aberrant pathology which are anticipated to promote replication of SARS-CoV-2 infection and would account for novel COVID-19 related death. Given SIP related pathogenetic inflammation and association of SIPR1 and ACE2 linked signaling, it is likely that SIP, despite its antibacterial potential [29], might not be effective in controlling SARS-CoV-2 infection. Hence blocking SIP response either by enhancing SIP lyase activity [30] or inhibiting its binding to its receptor by use of analogue known as FTY720 (Fingolimod) [31,32] may modulate the pathogenesis of novel COVID-19 cases. Currently, FTY720 is being explored in the Phase-2 clinical trial against COVID-19 patients (NCT04280588, MRCTA, ECAFH of FMU), and results are still awaited. Due to immunosuppressive nature FTY720 is only expected to lower down the hyper-inflammatory response and afford symptomatic/temporary relief and unlikely to afford clearance of infection [33] in novel COVID-19 cases.

2. Sphingosine -1-phosphate (SIP) / Sphingosine kinase (SK) and viral infections

A plethora of evidence suggested that SIP promotes the pathogenesis in several inflammatory and tumor diseases. Although hundreds of sphingolipid species have been identified in the past, SIP / Ceramide [7-9] are the two best-studied sphingolipid derivatives studied in the context of respiratory diseases [10-12]. In view of this, we here discussed various approaches of how modulating sphingolipids derivatives may help in controlling SARS-CoV-2 infection in COVID-19 patients. SIP is known to influence mast cells’ allergic response and other alveolar cells like macrophages and epithelial cells, which serve as a significant barrier for various pathogens and are expected to be relevant for controlling pathogens. In this context, studies have demonstrated the association of sphingolipids with viral tropism, viral-attachment, viral-replication, and viral-pathogenicity of several viral infections [13, 14]; thus, sphingolipids indeed represent one of the potential targets for controlling the viral disease. On account of this we here discussed the significance of sphingolipid-based interventions for controlling SARS-CoV-2 infection, developing effective therapeutics for controlling the novel COVID-19 disease. Furthermore, several studies have suggested that sphingolipid metabolites are involved in the replication of Influenza A Virus (IAV). Increased SK1 activity in the IAV infected promotes the synthesis and stability of viral ribo-nucleoprotein complex [15] in the infected epithelial cells.

Several reports have demonstrated a correlation between increased turnover of SIP in virus-infected cells supporting viral replication in the host. Additionally, increased levels of SK1/SIP lead to activation of ERK-1/2 (extracellular signal-regulated kinases), MAPK (mitogen-activated protein kinases), and AKT signaling pathways, which further promote viral replication in the host. Most intriguingly, impeded expression of SK1 leads to a decrease in glycoproteins’ activity in the IAV infected cells [16]. Therefore, the perturbation in the biosynthesis or depletion of host sphingomyelin impairs viral maturation, budding, and release of the infected cells’ viral nuclear particle [16]. Therefore, the perturbation in the biosynthesis or depletion of host sphingomyelin impairs viral maturation, budding, and release [16] of the infected cells’ viral nuclear particle. Similarly, it was demonstrated that SK1 is critical for the nuclear export of viral proteins (NP, NS2, and M1) involved in transporting vRNPs from the nucleus to the cytoplasm. Later, Tafesse et al. projected that perturbation of host sphingomyelin biosynthesis inhibited the transport of influenza virus HA and NA to the cell surface, which in turn impaired viral maturation, budding, and release. Influenza virus activates multiple signal transduction pathways (ERK pathways) to make the intracellular environment extremely affordable for viral propagation [17]. Interestingly SK1/SIP is associated with the inhibition of ERK and NF-κB pathway (nuclear factor kappa-light-chain-enhancer of activated B cells) which are essential for viral replication [18] and nuclear transport of viral ribo-nucleoprotein complex respectively in the infected cell [19] and indicates that increased levels of SIP / SK1 enzymatic activity support virus infection in the host. On account of this, either pharmacological activation of SIP Lyase or inhibition of SK1 is likely to control replication of SARS-CoV-2 virus as well in COVID-19 patients. Like IAV, human cytomegalovirus (HCMV) increases SK1 activity which contributes to the efficient virus replication. Blockade of SK1 expression decreased the expression of immediate-early IE1 protein, over expression of same elevated the expression of IE1 proteins and virus particles [20]. Similarly, respiratory syncytial virus (RSV) increased the activity of SK1 and the mRNA expression of SK1 as well. Elevated activation of SK1 has shown to enhance RSV-induced activation of ERK MAPK and AKT signaling pathways which regulate the cell survival pathway upon infection. SARS-CoV2 interacts with angiotensin-converting enzyme 2 (ACE2) receptors on alveolar epithelial cells for its attachment and entry [21,22]. Since ACE2 / Angiotensin-II receptors and SIP receptor 1 (SIPR1) signaling is known to cooperate to promote IL-6 induced myopathy and fibrosis [23] in a mouse model cardiac hypertrophy. On the basis of this report, it is possible that a crosstalk of these receptors may contribute to fibrosis in COVID-19 patients as well. Interestingly, S1PR1 signaling is associated with Th1 / Th2 /17 responses [24,25] in context dependent manner. Apart from this, SIPR1 signaling promotes hypoxia, asthmatic reactions [26] and anti-inflammatory response [27,28] in cancer patients. On account of this and increased expression of SK1 and SIP turnover in the virus-infected host, it is logical to presume that increased SIP signaling is likely to promote SARS-CoV-2 infection / replication in COVID-19 patients and warrant investigation.

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3. Ceramide/Ceramide-1 Phosphate as proposed anti-Covid-19 agents

In view of proviral attributes of SIP, exploring other sphingolipid derivatives like Ceramide-1 Phosphate (CIP) with immune adjuvant and antiviral potential [34,35] may help the host in controlling the novel COVID-19 disease. Since free ceramide is potentially pro-apoptotic in nature, phosphorylated ceramide or CIP can be used for the management of disease pathology in COVID-19 patients. Unlike SIP, not much is known how CIP could influence the viral replication in host. In this context, one compelling study has demonstrated its potent anti-retroviral and immune augmenting potential [46] against HIV infection and on account of this, CIP is expected to qualify pharmacological criteria of being introduced/used as adjunct therapy against COVID-19 disease. In view of this, mobilizing CIP in COVID–19 patients seems to be appropriate strategies for interventions. Although there are various ways by which CIP could be enhanced in the COVID-19 patients for-affording therapy. However due to feasibility and toxicity issues, we here described two potential modalities that could be used as therapy components. One of those is to supplement infected host or patients with l-serine essential amino acid in conjunction with Palmitoyl CoA or its analogs (due to kidney clearance issue) for increased synthesis of ceramide [36-38] in their plasma. Another strategy is to use ceramide
attention. We strongly anticipate that C1P would promote the killing of infected cells and resolve infection in moderate to severely infected cases. On account of this, ceramide derivatives can be exploited as drug candidates for controlling SARS-CoV-2 against novel COVID-19 disease. Further synthesis by either L serine / Palmitoyl Co A ceramide analog [46] or macrophages [40] certainly have potential of augmenting required adaptive immunity for controlling SARS-CoV-2 virus in the host.

Taken together, we believe that enhancing the C1P gradient or its synthesis by either L serine / Palmitoyl Co A ceramide analog [46] or Ceramide kinase [47,48] is believed to augment required adaptive immunity [41,49,50] for controlling infection effectively as shown in Fig. 1b.

4. Conclusion and perspectives

We here propose that Sphingolipid derivatives are promising drug candidates for the management of novel COVID-19 disease. Furthermore, C1P based tailoring of Th1 effector immunity for the eradication of infection is a translationally viable approach and deserves immediate attention. We strongly anticipate that C1P would promote the killing of infected cells and resolve infection in moderate to severely infected cases. On account of this, ceramide derivatives can be exploited as drug candidates for controlling SARS-CoV-2 against novel COVID-19 disease.

Author contributions

HP conceived the idea and supervised the entire study. DJU, ORB, AKJ, contributed to the research. HP and BK: Critical analysis. HP and AJ wrote the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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References

[1] L. Sharma, H. Prakash, Sphingolipids are dual specific drug targets for the management of pulmonary infections: perspective, Front. Immunol. 8 (2017) 378.
[2] H. Sawai, Y.A. Hannun, Ceramide and sphingomyelinases in the regulation of stress responses, Chem. Phys. Lipids 102 (1–2) (1999) 141–147. Nov.
[3] A.H. Merrill Jr., S. Lingrell, E. Wang, M. Nikolova-Karakashian, T.R. Vales, D. E. Vance, Sphingolipid biosynthesis de novo by rat hepatocytes in culture. Ceramide and sphingomyelin are associated with, but not required for, very low density lipoprotein secretion, J. Biol. Chem. 270 (23) (1995) 13834–13841. Jun 9.
[4] T.D. Mullen, Y.A. Hannun, L.M. Obeid, Ceramide synthases at the centre of sphingolipid metabolism and biology, Biochem. J 441 (3) (2012) 789–802. Feb 1.
[5] C. Teng, H. Dong, L. Shi, Y. Deng, J. Mu, J. Zhang, et al., Serine palmitoyltransferase, a key enzyme for de novo synthesis of sphingolipids, is essential for male gametophyte development in Arabidopsis, Plant Physiol. 146 (3) (2008) 1322–1332. Mar.
[6] T.S. Worgall, Sphingolipid synthetic pathways are major regulators of lipid homeostasis, Adv. Exp. Med. Biol. 721 (2011) 139–148.
[7] N.C. Hall, C.A. Oskeritzian, S.W. Paugh, S. Milstien, S. Spiegel, Sphingolipid kinases, sphingosine 1-phosphate, apoptosis and diseases, Biochim. Biophys. Acta 1758 (12) (2006) 2016–2026. Dec.
[8] S. Spiegel, S. Milstien, The outs and the ins of sphingosine-1-phosphate in immunity, Nat. Rev. Immunol. 11 (6) (2011) 403–415. Jun.
[9] L. Arana, P. Gangoiti, A. Otero, M. Trueba, A. Gomez-Munoz, Ceramide and ceramide 1-phosphate in health and disease, Lipids Health Dis. 9 (2010) 15. Feb 5.
Mediated innate immune responses to influenza virus infection, J. Immunol. 199 (2017) 677–687. Jul 15.

[31] D. Papadopoulos, J. Rundle, P. Patel, I. Marshall, J. Stretton, R. Eaton, et al., FTY720 ameliorates MOG-induced experimental autoimmune encephalomyelitis by suppressing both cellular and humoral immune responses, J. Neurosci. Res. 88 (2010) 346–359. Feb 1.

[32] G. Penelas-Rivas, R. Dominguez-Perles, V. Brinkmann, M.L. Del Rio, A. Munoz-Luna, P. Ramirez-Romero, et al., FTY720 inhibits TH1-mediated allogeneic humoral immune response, Transplant Proc 37 (9) (2005) 4124–4126. Nov.

[33] K.B. Walsh, D. Marsolais, M.J. Welch, H. Rosen, M.B. Oldstone, Treatment with a sphingosine analog does not alter the outcome of a persistent virus infection, Virology 397 (2) (2010) 260–269. Feb 20.

[34] C.M. Finneegan, S.S. Rawat, A. Puri, J.M. Wang, F.W. Ruscetti, R. Blumenthal, Ceramide, a target for antiretroviral therapy, Proc. Natl. Acad. Sci. U. S. A. 101 (43) (2004) 15452–15457. Oct 26.

[35] C.J. Pritzl, V.J. Seo, C. Xia, M. Vijayan, Z.D. Stokes, B. Hahn, A. Munoz-Luna, Sphingolipids as potential therapeutic targets against influenza A induced cellular signal transduction pathways, J. Thorac. Dis. 5 (Suppl 2) (2013) S132–S141. Aug.

[36] P. Michael, D. Brabant, F. Bleiblo, C.V. Ramana, M. Rutherford, S. Khurana, et al., Intact sphingomyelin biosynthetic pathway is essential for intracellular transport of influenza virus glycoproteins, Proc. Natl. Acad. Sci. U. S. A. 110 (16) (2013) 6404–6411. Apr 16.

[37] Y. Hirabayashi, S. Furuya, Roles of l-serine and sphingolipid synthesis in brain development and neuronal survival, Prog. Lipid Res. 47 (3) (2008) 188–203. May.

[38] B. Weiss, W. Stoffel, Human and murine serine-palmitoyl-CoA transferase-cloning, expression and characterization of the key enzyme in sphingolipid synthesis, Eur. J. Biochem. 249 (1) (1997) 239–247. Oct 1.

[39] P. Rovina, C. Graf, F. Bormancin, Modulation of ceramide metabolism in mouse primary macrophages, Biochem. Biophys. Res. Commun. 399 (2) (2010) 150–154. Aug 20.

[40] L. Arana, P. Gangoiti, A. Ouro, I.G. Rivera, M. Ordonez, M. Trueba, et al., Generation of reactive oxygen species (ROS) is a key factor for stimulation of macrophage proliferation by ceramide 1-phosphate, Exp. Cell. Res. 318 (4) (2012) 350–360. Feb 15.

[41] A. Ouro, L. Arana, P. Gangoiti, I.G. Rivera, M. Ordonez, M. Trueba, et al., Ceramide 1-phosphate stimulates glucose uptake in macrophages, Cell. Signal. 25 (4) (2013) 786–795. Apr.

[42] P. Gangoiti, M.H. Granado, S.W. Wang, J.Y. Kong, U.P. Steinbrecher, A. Gomez-Munoz, Ceramide 1-phosphate stimulates macrophage proliferation through activation of the PI3-kinase/PKB, JNK and ERK1/2 pathways, Cell Signal. 20 (4) (2008) 726–736. Apr.

[43] A. Gomez-Munoz, Ceramide-1-phosphate: a novel regulator of cell activation, FEBS Lett. 562 (1–3) (2004) 5–10. Mar 26.

[44] V. Hinkovska-Galcheva, L.A. Boxer, A. Kindzeliski, M. Hiraoka, A. Abe, S. Goparaj, et al., Ceramide 1-phosphate, a mediator of phagocytosis, J. Biol. Chem. 280 (28) (2005) 26612–26621. Jul 15.

[45] C.J. Pritzl, V.J. Seo, C. Xia, M. Vijayan, Z.D. Stokes, B. Hahn, A. Munoz-Luna, Sphingolipids as potential therapeutic targets against influenza A induced cellular signal transduction pathways, J. Thorac. Dis. 5 (Suppl 2) (2013) S132–S141. Aug.

[46] P. Michael, D. Brabant, F. Bleiblo, C.V. Ramana, M. Rutherford, S. Khurana, et al., Intact sphingomyelin biosynthetic pathway is essential for intracellular transport of influenza virus glycoproteins, Proc. Natl. Acad. Sci. U. S. A. 110 (16) (2013) 6404–6411. Apr 16.

[47] Y. J. Seo, S. Bae, S. Alexander, et al., Control of inflammatory responses by ceramide, sphingosine 1-phosphate-metabolizing enzymes control influenza virus propagation and viral cytopathogenicity, J. Virol. 84 (16) (2010) 8124–8131. Aug.

[48] T. Schulze, S. Golfier, C. Tabeling, K. Rabel, M.H. Graler, M. Witzenrath, et al., Sphingosine-1-phosphate receptor 4 (S1P(4)) deficiency profoundly affects dendritic cell functions and asthma and its regulation by non-coding RNA, Front. Immunol. 8 (2017) 587.

[49] V. Nadella, I. Sharma, P. Kumar, P. Gupta, U.D. Gupta, S. Tripathi, et al., Sphingosine-1-phosphate (S1P) promotes differentiation of naive macrophages and enhances protective immunity against Mycobacterium tuberculosis, Front. Immunol. 10 (2019) 3085.