frontiers | Frontiers in Physiology

EDITORIAL
published: 28 April 2022
doi: 10.3389/fphys.2022.906205

Editorial: Significance of Cellular Lipids for Viral Replication and Pathogenesis

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Keywords: lipid droplets, sphingolipids, cholesterol, viral replication, viral entry, broadspectrum antiviral therapy

Editorial on the Research Topic

Significance of Cellular Lipids for Viral Replication and Pathogenesis

Cellular lipids and their metabolism have increasingly been recognized as essential for various steps of viral replication cycles, including viral entry, genome transcription and replication, particle assembly and egress. These cellular lipids include various structural molecules, such a gangliosides, phospholipids, sterols and sphingolipids, and are localized in cellular membranes and lipid droplets (LDs). Alterations of lipid homeostasis can promote or block viral replication and are often accompanied by the production of pro-inflammatory cytokines. Therefore, cellular lipids and their metabolites are considered to be attractive targets for the development of new broad-spectrum antiviral therapies.

The biosynthesis of intracellular fatty acids and sterols as well as their metabolic pathways are well researched (Walther and Farese, 2012; Crawford and Desselberger, 2016). Lipid droplets (LDs) are major storage organelles of neutral lipids, such as triacylglycerols and cholesterol esters, and act as vehicles for intracellular transport (Walther et al., 2017). These organelles, and other lipids, are also important for the replication of various RNA viruses such as hepatitis C viruses, Dengue viruses (Chatel-Chaix and Bartenschlager, 2014; Bang et al., 2019), species A rotaviruses (Cheung et al., 2010), picornaviruses (Belov and van Kuppeveld, 2019; Laufman et al., 2019), noroviruses (Doerflinger et al., 2017), SARS-CoV-2 (Dias et al., 2020; Nardacci et al., 2021; Theken et al., 2021) and some DNA viruses such as Marek's disease virus (Boodhoo et al., 2019). However, the specific mechanisms by which these viruses interact with the cellular lipidome remain incompletely understood.

The roles of cellular lipids in viral replication and pathogenesis and their potential to be developed as drug targets were highlighted in seven articles in the Research Topic by *Frontiers in Physiology*.

Avota et al. assessed the various roles played by sphingolipids during the different steps of viral replication (virus attachment and entry, viral replication, morphogenesis and budding), updating earlier reviews (Schneider-Schaulies and Schneider-Schaulies, 2015; Schneider-Schaulies et al., 2021). They also discuss the possibility to repurpose inhibitors of sphingolipid metabolism already in clinical use for treatment of viral infections.

Similarly, Farfan-Morales et al. discuss the use of FDA-approved lipid-lowering drugs as host cell-targeted antivirals against flavivirus disease caused by Dengue and Zika viruses. In this context the contribution by Vial et al. is of interest. In mosquitoes, which act as vectors for various human flavivirus infections, the phospholipidome is upregulated during virus replication. This finding may lead to the development of novel, host-specific antivirals with the aim to block transmission to the human host.

Other researchers highlighted the potential of various lipid metabolic pathways as antiviral targets. Cellular cholesterol, as a component of cellular lipid rafts has recently gained much attention

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Specialty section:
This article was submitted to Lipid and Fatty Acid Research, a section of the journal Frontiers in Physiology

Received: *28 March 2022*
Accepted: *11 April 2022*
Published: *28 April 2022*

Citation:
Desselberger U, Pohl CH and O'Neill HG (2022) Editorial: Significance of Cellular Lipids for Viral Replication and Pathogenesis. Front. Physiol. 13:906205. doi: 10.3389/fphys.2022.906205

as being required for cellular entry of many enveloped and non-enveloped viruses (Ripa et al., 2021; Sanders et al., 2021). In the review by Glitscher and Hildt, the fact that viruses redistribute cellular cholesterol during infection was emphasised. Furthermore, it was proposed that strategies to manage the distribution of cellular cholesterol during viral infection, rather than a global reduction of cholesterol metabolism, be investigated for the development of broad-spectrum antivirals. Measles virus replication in primary human lymphocytes was found to be significantly reduced by inhibitors of ceramidase and sphingosine kinases 1 and 2 (Chithelen et al.), which correlated with the blockage of the phosphorylation of cellular translation factors.

Lipid droplets are important for rotavirus replication and take part in the formation of viral factories, termed viroplasms (Cheung et al., 2010). Crawford et al. reported that a recombinant rotavirus A strain containing a mutant NSP2 protein exhibits delayed viroplasm formation. They observed an early interaction of NSP2 with phosphorylated perilipin 1 located on LDs, thus dissecting part of the molecular mechanism of viroplasm-LD interaction during rotavirus replication. Following rotavirus infection, Sander et al. observed an increase in the production of the arachidonic acid metabolite, the eicosanoid prostaglandin E_2. This metabolite has been implicated in various steps of viral replication, including viral binding to cellular receptors, viral gene expression, increase in pro-inflammatory cytokines and the production and release of nascent virions (Sander et al., 2017). In the current study, co-localization between prostaglandin E_2 and viroplasms was shown. Inhibitors of prostaglandin E_2 synthesis, such as indomethacin, reduced the yield of infectious viral progeny by approximately 1 log step. This finding points to a role of prostaglandin E_2 in enhancement of rotavirus attachment and internalisation.

Viral factories have recently been recognized as liquid-liquid phase separation (LLPS)-driven protein-RNA condensates (Etibor et al., 2021; Geiger et al., 2021; Papa et al., 2021) which change their material properties over time and can interact with LDs at later stages of infection. Details of the interaction of the biomolecular condensates with cellular compounds (LDs, tubulin, and others) remain to be elucidated.

Up to now, the interaction of the cellular lipidome with replication steps of mammalian viruses has been explored mainly *in vitro*. Translational research of these relationships in intestinal organoids (Saxena et al., 2015; Ettayebi et al., 2016) and suitable animal models is very much at the beginning but is promising for the development of broad-spectrum antiviral therapy. However, this pathway may not always be straightforward. In the search of licensed drugs for repurposing to treat COVID-19 disease, it was recently found that most of the drugs with antiviral activity were cationic amphiphilic compounds associated with the development of phospholipidosis in cells and organs, thus confounding this avenue of drug discovery (Tummino et al., 2021). While interference with lipid metabolism may hold the potential for the development of broad-spectrum antiviral therapies, this is a complex approach which will require further in-depth basic research.

AUTHOR CONTRIBUTIONS

UD prepared the first draft; CP and HO reviewed and edited. All authors approved the final submitted version.

REFERENCES

Bang, B.-R., Li, M., Tsai, K.-N., Aoyagi, H., Lee, S.-A., Machida, K., et al. (2019). Regulation of Hepatitis C Virus Infection by Cellular Retinoic Acid Binding Proteins through the Modulation of Lipid Droplet Abundance. *J. Virol.* 93 (8), e02302–18. doi:10.1128/JVI.02302-18

Belov, G. A., and van Kuppeveld, F. J. M. (2019). Lipid Droplets Grease Enterovirus Replication. *Cell Host & Microbe* 26 (2), 149–151. doi:10.1016/j.chom.2019.07.017

Boodhoo, N., Kamble, N., Kaufer, B. B., and Behboudi, S. (2019). Replication of Marek's Disease Virus Is Dependent on Synthesis of De Novo Fatty Acid and Prostaglandin E 2. *J. Virol.* 93 (13), e00352–19. doi:10.1128/JVI.00352-19

Chatel-Chaix, L., and Bartenschlager, R. (2014). Dengue Virus- and Hepatitis C Virus-Induced Replication and Assembly Compartments: the Enemy Inside-Caught in the Web. *J. Virol.* 88 (11), 5907–5911. doi:10.1128/JVI.03404-13

Cheung, W., Gill, M., Esposito, A., Kaminski, C. F., Courousse, N., Chwetzoff, S., et al. (2010). Rotaviruses Associate with Cellular Lipid Droplet Components to Replicate in Viroplasms, and Compounds Disrupting or Blocking Lipid Droplets Inhibit Viroplasm Formation and Viral Replication. *J. Virol.* 84 (13), 6782–6798. doi:10.1128/JVI.01757-09

Crawford, S. E., and Desselberger, U. (2016). Lipid Droplets Form Complexes with Viroplasms and Are Crucial for Rotavirus Replication. *Curr. Opin. Virol.* 19, 11–15. doi:10.1016/j.coviro.2016.05.008

Dias, S. S. G., Soares, V. C., Ferreira, A. C., Sacramento, C. Q., Fintelman-Rodrigues, N., Temerozo, J. R., et al. (2020). Lipid Droplets Fuel SARS-CoV-2 Replication and Production of Inflammatory Mediators. *Plos Pathog.* 16 (12), e1009127. doi:10.1371/journal.ppat.1009127

Doerflinger, S. Y., Cortese, M., Romero-Brey, I., Menne, Z., Tubiana, T., Schenk, C., et al. (2017). Membrane Alterations Induced by Nonstructural Proteins of Human Norovirus. *Plos Pathog.* 13 (10), e1006705. doi:10.1371/journal.ppat.1006705

Etibor, T., Yamauchi, Y., and Amorim, M. (2021). Liquid Biomolecular Condensates and Viral Lifecycles: Review and Perspectives. *Viruses* 13 (3), 366. doi:10.3390/v13030366

Ettayebi, K., Crawford, S. E., Murakami, K., Broughman, J. R., Karandikar, U., Tenge, V. R., et al. (2016). Replication of Human Noroviruses in Stem Cell-Derived Human Enteroids. *Science* 353 (6306), 1387–1393. doi:10.1126/science.aaf5211

Geiger, F., Acker, J., Papa, G., Wang, X., Arter, W. E., Saar, K. L., et al. (2021). Liquid-liquid Phase Separation Underpins the Formation of Replication Factories in Rotaviruses. *EMBO J.* 40 (21), e107711. doi:10.15252/embj.2021107711

Laufman, O., Perrino, J., and Andino, R. (2019). Viral Generated Inter-organelle Contacts Redirect Lipid Flux for Genome Replication. *Cell* 178 (2), 275–289. e16. doi:10.1016/j.cell.2019.05.030

Nardacci, R., Colavita, F., Castilletti, C., Lapa, D., Matusali, G., Meschi, S., et al. (2021). Evidences for Lipid Involvement in SARS-CoV-2 Cytopathogenesis. *Cell Death Dis* 12 (3), 263. doi:10.1038/s41419-021-03527-9

Papa, G., Borodavka, A., and Desselberger, U. (2021). Viroplasms: Assembly and Functions of Rotavirus Replication Factories. *Viruses* 13 (7), 1349. doi:10.3390/v13071349

Ripa, I., Andreu, S., López-Guerrero, J. A., and Bello-Morales, R. (2021). Membrane Rafts: Portals for Viral Entry. *Front. Microbiol.* 12, 631274. doi:10.3389/fmicb.2021.631274

Sander, W. J., O'Neill, H. G., and Pohl, C. H., (2017). Prostaglandin E2 as a modulator of viral infections. *Front. Physiol.* 8:89. doi:10.3389/fphys.2017.00089

Sanders, D. W., Jumper, C. C., Ackerman, P. J., Bracha, D., Donlic, A., Kim, H., et al. (2021). SARS-CoV-2 Requires Cholesterol for Viral Entry and Pathological Syncytia Formation. *Elife* 10, e65962. doi:10.7554/eLife.65962

Saxena, K., Blutt, S. E., Ettayebi, K., Zeng, X.-L., Broughman, J. R., Crawford, S. E., et al. (2016). Human Intestinal Enteroids: a New Model to Study Human Rotavirus Infection, Host Restriction, and Pathophysiology. *J. Virol.* 90 (1), 43–56. doi:10.1128/JVI.01930-15

Schneider-Schaulies, J., and Schneider-Schaulies, S. (2015). Sphingolipids in Viral Infection. *Biol. Chem.* 396 (6-7), 585–595. doi:10.1515/hsz-2014-0273

Schneider-Schaulies, S., Schumacher, F., Wigger, D., Schöl, M., Waghmare, T., Schlegel, J., et al. (2021). Sphingolipids: Effectors and Achilles Heals in Viral Infections? *Cells* 10 (9), 2175. doi:10.3390/cells10092175

Theken, K. N., Tang, S. Y., Sengupta, S., and FitzGerald, G. A. (2021). The Roles of Lipids in SARS-CoV-2 Viral Replication and the Host Immune Response. *J. Lipid Res.* 62, 100129. doi:10.1016/j.jlr.2021.100129

Tummino, T. A., Rezelj, V. V., Fischer, B., Fischer, A., O'Meara, M. J., Monel, B., et al. (2021). Drug-induced Phospholipidosis Confounds Drug Repurposing for SARS-CoV-2. *Science* 373 (6554), 541–547. doi:10.1126/science.abi4708

Walther, T. C., Chung, J., and Farese, R. V., Jr (2017). Lipid Droplet Biogenesis. *Annu. Rev. Cel Dev. Biol.* 33, 491–510. doi:10.1146/annurev-cellbio-100616-060608

Walther, T. C., and Farese, R. V., Jr (2012). Lipid Droplets and Cellular Lipid Metabolism. *Annu. Rev. Biochem.* 81, 687–714. doi:10.1146/annurev-biochem-061009-102430

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