UJEMI PERSPECTIVES

# Lipid droplets: A hallmark of SARS-CoV-2 infection and a potential target for novel antiviral therapeutics

Lana Hui

Department of Microbiology and Immunology, University of British Columbia, Vancouver, British Columbia, Canada

**SUMMARY** Since its emergence, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has infected over 110.7 million people and killed over 2.4 million people worldwide. Currently, Remdesivir is the only antiviral approved by the Food and Drug Administration (FDA) to treat the disease caused by SARS-CoV-2, coronavirus disease 2019 (COVID-19). With millions of new COVID-19 cases reported weekly, efficient, and broad-acting antiviral treatments are urgently needed. Host lipid metabolic reprograming and the formation of lipid droplets (LDs) may play a role in SARS-CoV-2 replication and pathogenesis—opening new perspectives for therapeutic strategies against COVID-19. This paper will review the current knowledge on LDs in the SARS-CoV-2 lifecycle and its potential functions in viral replication, assembly, and pro-inflammatory cell moderation. This paper will also highlight key research areas in the field that remain to be understood, including, (i) the possible moonlighting activities of LD-associated viral proteins in the host-cell nucleus of SARS-CoV-2 infected cells, (ii) the potential ability for SARS-CoV-2 to escape or exploit autophagic machinery to enhance viral fitness and survival, and (iii) the impact of diet on one's susceptibility to SARS-CoV-2 infection. Overall, a better understanding of the SARS-CoV-2 lifecycle and host cell interactions will clarify mechanisms of infection at various levels, inform the design of novel and effective therapeutics and vaccines, and reduce the impact of the COVID-19 pandemic on public health.

## INTRODUCTION

The rapid spread of coronavirus disease 2019 (COVID-19) in a global pandemic has crippled the world, leaving lasting social, economic, and health consequences for years to come (1). The etiological agent of COVID-19, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), is a novel human zoonotic pathogen belonging to the *Betacoronavirus* genus of the subfamily *Orthocoronavirinae* in the *Coronaviridae* family (2, 3). SARS-CoV-2 is an enveloped, non-segmented, single stranded positive-sense RNA ((+)ssRNA) virus that, similar to other highly pathogenic human coronaviruses, induces aberrant host immune responses associated with respiratory diseases and, in severe cases, can lead to acute respiratory distress syndrome (ARDS), cytokine storm, and case fatality (4, 5). Unlike previously known coronaviruses like SARS- and Middle East respiratory syndrome (MERS)-CoV, however, epidemiological analyses have revealed that SARS-CoV-2 is more infectious and transmissible among individuals (5); thus, a better understanding of the SARS-CoV-2 lifecycle to develop safe, and effective treatments to contrast the pathogenicity of SARS-CoV-2 are desperately needed.

The hijacking and manipulation of host cell metabolic pathways are shared features of the lifecycles of many human enveloped (+)ssRNA viruses, including that of *Flaviviridae, Reoviridae*, and *Coronaviridae* families (1, 6-9). In fact, among the cellular adaptation mechanisms that (+)ssRNA viruses may adopt, lipid modulation has been highlighted in *all* major steps of viral infection (10, 11). Such adaptations include alterations in fatty acid metabolism, sterol biosynthesis, synthesis of specific phosphoinositides, and utilization of lipid stores, allowing viruses to obtain energy and substrates to benefit their replication and survival (12, 13). Although the detailed mechanisms by which such lipid modulations occur in *Coronaviridae* remain to be resolved (14), a new body of research has pointed to lipid droplet (LD) formation as a hallmark of host lipid reprogramming, viral replication, and

**Published Online:** September 2021

**Citation:** Lana Hui. 2021. Lipid droplets: A hallmark of SARS-CoV-2 infection and a potential target for novel antiviral therapeutics. UJEMI Perspectives 5:1-8

**Editor:** François Jean (Ph.D.), University of British Columbia



Address correspondence to Lana Hui

lanahui@alumni.ubc.ca

pathogenesis, illuminating LDs as potential targets for broad-acting therapeutic agents against SARS-CoV-2.

Lipid droplets are highly conserved intracellular organelles present in most cells (6). They are composed of neutral lipids such as triacylglycerols (TAGs), cholesteryl esters (CEs), fatty acids (FAs), and a surrounding phospholipid monolayer (6, 15, 16). Both cytoplasmic (cLDs) and nuclear LDs (nLDs) have been observed in eukaryotic cells originating from the endoplasmic reticulum and inner nuclear membrane, respectively (17, 18). Extracellular LDs (eLDs), released by virally-infected cells, have also been observed, suggesting a role for eLDs in viral pathogenesis with respect to the extracellular milieu (19). Previously regarded as merely hubs for fat storage, LDs are now known to be central to a variety of other cellular functions, including lipid homeostasis, protein storage, the immune response, and the production of proinflammatory molecules such as eicosanoids (1, 6, 20, 21). Despite the potential protective roles of LDs against intracellular pathogens such as viruses, however, many (+)ssRNA viruses have also been shown to extensively manipulate LDs as substrates for their energy and as platforms for their replication and assembly, including SARS-CoV-2 (2, 22, 23).

Recent works have demonstrated that SARS-CoV-2 is capable of upregulating lipid metabolism, resulting in the accumulation of LDs in virally infected cells (2). Induction of SARS-CoV-2 infection in human peripheral blood mononuclear cells (PBMCs) *in vitro* not only demonstrated a buildup of LDs in infected cells, but also upregulated various proteins involved in host lipid metabolism, including cluster of differentiation 36 (CD36), peroxisome proliferator-activated receptor gamma (PPAR-γ), sterol regulatory element-binding protein-1 (SREBP-1), and acyl-CoA:diacylglycerol acyltransferase-1 (DGAT-1), thus enhancing lipid uptake and promoting LD formation in SARS-CoV-2 infection (2). Moreover, increased LD accumulation was reported in monocytes directly from COVID-19 patients when compared to healthy volunteers, further suggesting that SARS-CoV-2 may modulate cellular lipid metabolism in favour of an increased lipid biogenesis and lipid remodelling phenotype *in vivo* (2). When LD biogenesis was inhibited with a pharmacological inhibitor of DGAT-1, an enzyme required for TAG synthesis, viral replication, proinflammatory mediator production, and cell death decreased in human pulmonary cells (A549 cell line) and monocytes (2). Therefore, targeting DGAT-1, or any of the other upregulated lipid metabolism proteins, may represent crucial opportunities for indirect-acting antiviral interventions (Fig. 1). Additional evidence demonstrating the close association of LDs with SARS-CoV-2 viral particles and dsRNA also suggests that LDs may function as a replication platform for SARS-CoV-2 in VERO E6 cells (2). Altogether, these findings reveal previously unidentified roles for LDs in the SARS-CoV-2 lifecycle, and provide new insights for broad-spectrum, indirect-acting antiviral targets.

## PROPOSED RESEARCH QUESTIONS

Given the threat of COVID-19 on global public health, the development of safe and effective therapeutics is urgently needed. Currently, Remdesivir, a viral RNA-dependent RNA polymerase (RdRp) inhibitor, is the only antiviral approved by the Food and Drug Administration (FDA) for use against COVID-19 (24). Thus. considering other strategies to combat COVID-19 in the long-term and minimize its burden of disease, is critical. Targeting LD biogenesis may represent an important opportunity for indirect-acting antiviral intervention. Not only would inhibiting LD formation potentially provide broad-spectrum antiviral activity against many other (+)ssRNA viruses that exploit similar mechanisms, but it would also ensure minimal cytotoxicity, since LDs are upregulated products of viral infection.

Therefore, a better understanding of LDs in the SARS-CoV-2 lifecycle is needed to clarify the feasibility of targeting LDs for antiviral treatment. To advance the knowledge in this field, I propose three key areas of future research: first, the function of nLDs in SARS-CoV-2 pathogenesis; next, the potential ability for SARS-CoV-2 to exploit the autophagy pathway to maintain LD levels in the cell and benefit its replication and survival; finally, the possible relationship between host diet and LD biogenesis and, subsequently, host susceptibility to SARS-CoV-2 infection.

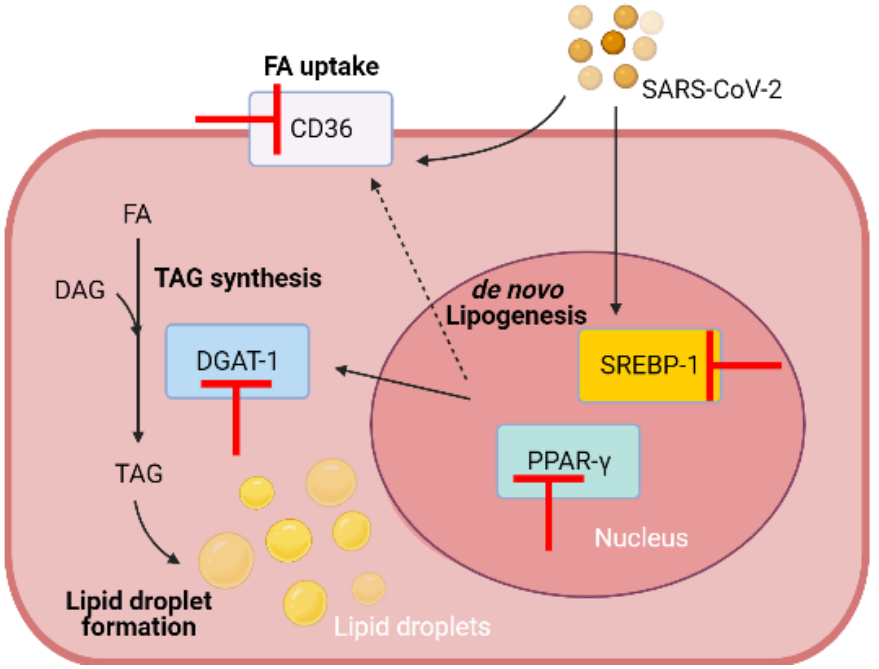


**FIG. 1 Upregulated proteins involved in LD formation upon SARS-CoV-2 infection in human monocytes are potential targets for indirect-acting antivirals.** SREBP-1 and PPAR-γ, the major transcriptional factors involved in lipogenesis, DGAT-1, the enzyme responsible for TAG synthesis, and CD36, the membrane receptor regulated by PPAR-γ that functions in FA uptake, are host lipid metabolism factors that are upregulated in SARS-CoV-2 infection. They may contribute to the accumulation of LDs observed in SARS-CoV-2 infected human monocytes and therefore represent potential targets for antiviral intervention. Adapted from "Lipid droplets fuel SARS-CoV-2 replication and production of inflammatory mediators" by Dias SSG, Soares VC, Ferreira AC, et al. PLoS Pathog. 2020. Fig. 1, SARS-CoV-2 infection modulates the lipid metabolism in human monocytes; p. 4. Created with BioRender.com.

## PROPOSED PROJECT NARRATIVE

**Are there potential moonlighting activities for LD-associated viral proteins in the nucleus of cells infected with SARS-CoV-2?** Although LDs are found predominantly in the cytoplasm, they have recently been detected in the nucleus as well and have been hypothesized to function similar to cLDs: as lipid stores for membrane expansion in the cell or scaffolding platforms for proteins (6, 25). However, I posit that there may be a potential moonlighting mechanism for nLDs, whereby SARS-CoV-2 may manipulate them to benefit viral replication and assembly. Specifically, trafficking of the viral nucleocapsid (N) protein to nLDs could increase protein stability and half-life within the nucleus, thus promoting SARS-CoV-2 survival within the host (6).

Like most enveloped RNA viruses, replication of SARS-CoV-2 and other coronaviruses occurs in the cytoplasm (26). However, the N proteins of many cytoplasmic RNA viruses have been shown to transiently localize to the nucleus/nucleolus (27). The N protein is responsible for binding tightly to the genomic RNA, facilitating RNA packaging, and, in some cases, serving as a nucleic acid chaperone in the cytoplasm (27). Although there is limited information about the function of the viral N protein in the nucleus, some evidence suggests it may support successful viral replication by interfering with or inhibiting the host interferon (IFN) antiviral response, or by disrupting host cell division (28, 29). Additionally, the nuclear localization sequence (NLS) of the N protein may predict high case fatality rates (CFR) of coronaviruses (30). The observation that enhanced NLS sequences—marked by the accumulation of positive charges in the amino acids comprising the NLS—correlates with high-CFR strains suggests that the N protein could be a crucial determinant of coronavirus pathogenicity (30, 31).

Thus, the hijacking of nLDs may be of critical importance for protecting the SARS-CoV-2 N protein in the nucleus and driving viral replication and suppression of host defense responses. Future work could further elucidate this association using immunofluorescent staining against the N protein and observing whether the protein localizes closely with nLDs in the nucleus. A better understanding of the relationship between nucleocapsid trafficking and nLDs would help clarify the SARS-CoV-2 lifecycle and host-cell interactions, as well as provide important insights and perspectives for putative antivirals which are, currently, of great need.

**What is the mechanism for LD catabolism in SARS-CoV-2 infection?** To date, very little is known about LD catabolism in SARS-CoV-2 infection. While LD biogenesis has been

shown to be upregulated in infection, promoting the formation and accumulation of LDs (2), the temporalities of LD degradation in SARS-CoV-2 infection remain unclear.

Autophagy comes from the Greek word meaning "self-eating" (32). It is a tightly regulated, routine mechanism used by cells to maintain homeostasis; thus, it is typically enhanced when homeostasis is compromised by stressful conditions such as lack of nutrients or oxygen, DNA damage, reactive oxygen species, or intracellular pathogens (33). During autophagy, double-membrane vesicles called autophagosomes sequester organelles, proteins, or portions of the cytoplasm to be delivered to the lysosome (34). Once autophagosomes fuse with the lysosome, autolysosomes form, and the packaged intracellular cargo is processed and degraded by specific enzymes within these compartments (32). Lipophagy refers to a specific form of autophagy that degrades LDs for the purposes of mobilizing free fatty acids for energy, managing the quality control of LD-targeted proteins, and maintaining lipid homeostasis (35).

By targeting viral particles or LDs to lysosomes within the autophagy pathway and stimulating the hosts' immune response, autophagy may serve a protective role in counteracting viral infections (32). However, certain viruses have also been able to neutralize lysosomal degradation and/or exploit the autophagy pathway to survive and replicate (32). In fact, (+)ssRNA viruses such as poliovirus, rhinovirus 2, and rhinovirus 14, have been shown to induce the production of double-membraned vesicles and subvert constituents of the autophagy pathway to form membranous platforms for the assembly of their RNA replication complexes (36). Heptatitis C virus (HCV), as another example, has also been suggested to hijack autophagy proteins to support translation of its HCV RNA and trigger viral replication (37). Nidovirales, on the other hand, appears to have the ability to manipulate autophagy as a double-edged sword, utilizing the products of autophagy for their synthesis, while exploiting autophagy to evade viral degradation at the same time (38).

With regards to coronaviruses, while other betacoronaviruses such as the murine hepatitis virus (MHV) have been shown to harness the autophagy pathway for replication, preliminary evidence has revealed that SARS-CoV-2 inhibits autophagy through AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin complex 1 (mTORC1) downregulation, therefore preventing degradation of viral product and, likely, LD degradation as well (39, 40). Other findings have shown that autophagy promoters such as spermidine, niclosamide, and nitazoxanide have an effect against SARS-CoV-2 in *in vitro* experiments (41, 42). This is in line with the observation that lipophagy does not seem to be active in SARS-CoV-2 infection, which may account for the buildup and accumulation of LDs observed in infected cells (2).

Thus, the observation that SARS-CoV-2 seems to favour a lipid-rich environment provides key insights into the feasibility of interfering with lipid biogenesis or boosting the lipophagy pathway as potential antiviral mechanisms. More validated research is needed in this field to conclusively determine the connection between viral infection, LD formation, and autophagy/lipophagy to inform the use of such interventions against SARS-CoV-2.

**Could diet impact LD biogenesis and susceptibility to SARS-CoV-2 infection?** Given that SARS-CoV-2 appears to favour a lipid-rich intracellular environment to promote its replication and survival, the question begs, then, whether diet and fat consumption may influence host susceptibility to SARS-CoV-2 infection, and whether our daily lifestyle choices—such as what we eat—may explain differences in rates of infection around the globe.

During nutrient surplus, such as in conditions of excess caloric intake, LDs uptake neutral lipids, usually in the form of triacylglycerols and sterol esters (25, 43). Through processes such as *de novo* lipogenesis, lipolysis, and lipophagy, LDs alternate between periods of growth and degradation, with these processes closely reflecting cellular metabolism and cycles of nutrient availability (25, 43). LDs also function to prevent lipotoxicity by buffering potentially toxic lipids, and have critical roles in minimizing oxidative stress (25). However, several diseases have been associated with excess accumulation of LDs, including obesity, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and cardiovascular diseases (44, 45). Many of these chronic diseases—notably, obesity, diabetes, and cardiovascular diseases—are also risk factors and comorbidities for severe COVID-19 infection (46, 47). Thus, this suggests that there may be a connection between diet, LDs, and susceptibility to COVID-19 disease.

In mice, obesity due to genetic mutations or a high-fat diet leads to increased numbers of LDs in hepatocytes (48). Interestingly, these processes are often followed by activation of ER stress, which has been found to trigger a positive feedback loop involving the activation of a lipogenic gene expression program in the liver (49, 50). It has also been suggested that ER stress may additionally trigger inflammatory responses, thus further increasing insulin resistance and lipid biogenesis (51). This provides additional evidence for the possible association between obesity, diet, and the accumulation of intracellular LDs.

Many of the reasons accounting for the large geographical variations in death rates linked to the COVID-19 pandemic remain unexplained, despite abundant research (52). Although the more relevant factors—seasonal variations, immunity, cross-immunity, intensity, type, onset, duration, and measures of protection—are often considered, other environmental factors like diet or nutrition should not be overlooked (53). Especially, given that obesity is a risk factor for severe COVID-19, studies on the impact of diet and nutrition should take on great importance, as it could significantly inform public health measures and minimize the burden of pandemic diseases such as COVID-19 on individuals. At a molecular level, this calls for more studies looking at chemically inducing LDs in human cell lines and observing if cells become more susceptible to viral infection and disease. At a population level, more cross-cultural observational studies with large, representative sample sizes are needed to ascertain the impact of diet and nutrition on lipid biogenesis and susceptibility to infection.

## CONCLUSIONS

As a global killer, SARS-CoV-2 and its associated disease, COVID-19, has severed the social, economic, and health ties of many individuals and societies around the world. The need for long-term solutions to reduce the burden of disease is great, considering there being only one currently FDA approved drug on the market against COVID-19, Remdesivir (24).

Recent works surrounding the biology of lipid droplets (LDs) and its suggested functions in viral replication and survival provide a potential solution to this problem. Having emerged as more than just organelles for lipid stores, LDs are critical intracellular sites for lipid homeostasis, immune responses, protein storage, and viral infections (1, 2, 6, 20, 21). In SARS-CoV-2 infected cells, an accumulation of LDs can be observed, as well as the upregulation of key proteins and transcription factors involved in LD biogenesis (2). Thus, it has been proposed that, like other (+)ssRNA viruses such as hepatitis C virus (HCV) and dengue virus (DENV), LD biogenesis may be circumvented by SARS-CoV-2 to enhance their replication and assembly (2, 6). As such, interfering with LD formation presents an exciting opportunity to develop novel, broad-spectrum, and indirect-acting antiviral therapeutics against COVID-19.

LDs, more specifically the pathways contributing to their formation, represent ideal targets for antiviral interference for three reasons. First, LDs are a highly conserved intracellular organelle; thus, targeting conserved host factors may produce broad-spectrum antiviral activity against multiple viral infections due to similar biological mechanisms across cell types and across viruses of the same genus or family (54). Second, compared to direct-acting antiviral interventions targeting viral elements, host cellular elements are much less prone to mutation (54). Given the high replication and mutation rate of viruses, long-term antiviral therapy should aim to minimize opportunities for viral mutations and, consequently, the development of drug resistance (54). Hence, targeting host lipid metabolism presents an attractive solution for the long-term treatment of viral diseases such as COVID-19 (54). Finally, targeting upregulated host lipid metabolism factors such as the enzyme DGAT-1 or transcription factors SREBP-1 and PPAR-γ may reduce the pleiotropic impact that an indirect-acting antiviral may otherwise have on cellular homeostasis (2, 55). Since LDs are a major metabolic pathway *in vivo*, striking the perfect balance between causing host toxicity and inhibiting viral pathogenesis is critical (54). By targeting upregulated factors, this issue may be minimized. Thus, altogether, LD biogenesis serves as an appealing approach to develop effective antiviral therapeutics against SARS-CoV-2.

Despite these major advances in elucidating the role of LDs in SARS-CoV-2 pathogenesis and assessing its feasibility as an antiviral target, there is still much to uncover about SARS-CoV-2 and its connection with LDs. Key areas of future research include: the potential moonlighting mechanism of LD-associated viral proteins including, but not limited to, the N

protein in the nucleus of the host cell; the mechanisms by which SARS-CoV-2 may exploit or suppress the autophagy pathway to benefit its replication and survival; and the extent that diet may influence LD biogenesis and susceptibility to SARS-CoV-2 infection. Further research in these key areas will be necessary to paint a clearer picture of the SARS-CoV-2 lifecycle, mechanisms of infection, and host cell interactions and inform the design of effective therapeutics to reduce the burden of COVID-19 on individuals, families, and societies worldwide.

## ACKNOWLEDGEMENTS

I would like to thank Dr. François Jean and teaching assistant Lynnea Carr for their guidance and support throughout the construction of this manuscript. I would also like to thank my MICB 406 peers for their insights and support in the development of this manuscript. I would also like to acknowledge the Microbiology and Immunology Department at the University of British Columbia for providing the opportunity to engage in course-based undergraduate research experiences.

## REFERENCES

1. **Pagliari F, Marafioti MG, Genard G, Candeloro P, Viglietto G, Seco J, Tirinato L.** 2020. ssRNA Virus and Host Lipid Rearrangements: Is There a Role for Lipid Droplets in SARS-CoV-2 Infection? *Front Mol Biosci* **7**:578964.
2. **Dias SS, Soares VC, Ferreira AC, Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, Teixeira L, Nunes da Silva MA, Barreto E, Mattos M, de Freitas CS.** 2020. Lipid droplets fuel SARS-CoV-2 replication and production of inflammatory mediators. *PLoS Pathog* **16**(12):e1009127.
3. **Nardacci R, Colavita F, Castilletti C, Lapa D, Matusali G, Meschi S, Del Nonno F, Colombo D, Capobianchi MR, Zumla A, Ippolito G**. 2021. Evidences for lipid involvement in SARS-CoV-2 cytopathogenesis. *Cell Death & Disease* **12**(3):263.
4. **Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P.** 2020. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* **382**(8):727-33.
5. **Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E.** 2020. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect* **26**(6):729-34.
6. **Cloherty APM, Olmstead AD, Ribeiro CMS, Jean F**. 2020. Hijacking of Lipid Droplets by Hepatitis C, Dengue and Zika Viruses-From Viral Protein Moonlighting to Extracellular Release. *Int J Mol Sci* **21**(21).
7. **Villareal VA, Rodgers MA, Costello DA, Yang PL.** 2015. Targeting host lipid synthesis and metabolism to inhibit dengue and hepatitis C viruses. *Antiviral Res* **124**:110-21.
8. **Cheung W, Gill M, Esposito A, Kaminski CF, Courousse N, Chwetzoff S, Trugnan G, Keshavan N, Lever A, Desselberger U.** 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):6782-98.
9. **Coffey CM, Sheh A, Kim IS, Chandran K, Nibert ML, Parker JS.** 2006. Reovirus outer capsid protein micro1 induces apoptosis and associates with lipid droplets, endoplasmic reticulum, and mitochondria. *J Virol* **80**(17):8422-38.
10. **Stapleford KA, Miller DJ.** 2010. Role of cellular lipids in positive-sense RNA virus replication complex assembly and function. *Viruses* **2**(5):1055-68.
11. **Heaton NS, Randall G.** 2011. Multifaceted roles for lipids in viral infection. *Trends Microbiol* **19**(7):368-75.
12. **Pombo JP, Sanyal S.** 2018. Perturbation of Intracellular Cholesterol and Fatty Acid Homeostasis During Flavivirus Infections. *Front Immunol* **9**:1276.
13. **Mackenzie JM, Khromykh AA, Parton RG.** 2007. Cholesterol manipulation by West Nile virus perturbs the cellular immune response. *Cell Host Microbe* **2**(4):229-39.
14. **Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, Jiang C.** 2008. SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. *Cell Res* **18**(2):290-301.
15. **Tauchi-Sato K, Ozeki S, Houjou T, Taguchi R, Fujimoto T.** 2002. The surface of lipid droplets is a phospholipid monolayer with a unique Fatty Acid composition. *J Biol Chem* **277**(46):44507-12.
16. **Zweytick D, Athenstaedt K, Daum G.** 2000. Intracellular lipid particles of eukaryotic cells. *Biochimica et Biophysica Acta (BBA)-Reviews on Biomembranes* **1469**(2):101-20.
17. **Kassan A, Herms A, Fernández-Vidal A, Bosch M, Schieber NL, Reddy BJ, Fajardo A, Gelabert-Baldrich M, Tebar F, Enrich C, Gross SP.** 2013. Acyl-CoA synthetase 3 promotes lipid droplet biogenesis in ER microdomains. *J Cell Biol* **203**(6):985-1001.
18. **Romanauska A, Köhler A**. 2018. The Inner Nuclear Membrane Is a Metabolically Active Territory that Generates Nuclear Lipid Droplets. *Cell* **174**(3):700-15.e18.

19. **Wu YW, Mettling C, Wu SR, Yu CY, Perng GC, Lin YS, Lin YL.** 2016. Autophagy-associated dengue vesicles promote viral transmission avoiding antibody neutralization. *Scientific Reports* **6**(1):32243.
20. **Saka HA, Valdivia R.** 2012. Emerging Roles for Lipid Droplets in Immunity and Host-Pathogen Interactions. *Annual Review of Cell and Developmental Biology* **28**(1):411-37.
21. **Cermelli S, Guo Y, Gross SP, Welte MA.** 2006. The lipid-droplet proteome reveals that droplets are a protein-storage depot. *Curr Biol* **16**(18):1783-95.
22. **Samsa MM, Mondotte JA, Iglesias NG, Assunção-Miranda I, Barbosa-Lima G, Da Poian AT, Bozza PT, Gamarnik AV.** 2009. Dengue virus capsid protein usurps lipid droplets for viral particle formation. *PLoS Pathog* **5**(10):e1000632.
23. **Vieyres G, Pietschmann T.** 2019. HCV Pit Stop at the Lipid Droplet: Refuel Lipids and Put on a Lipoprotein Coat before Exit. *Cells* **8**(3).
24. **Panel C-TG.** 2021. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: National Institutes of Health [Available from: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/].
25. **Olzmann JA, Carvalho P.** 2019. Dynamics and functions of lipid droplets. *Nature Reviews Molecular Cell Biology* **20**(3):137-55.
26. **Millet JK, Whittaker GR.** 2018. Physiological and molecular triggers for SARS-CoV membrane fusion and entry into host cells. *Virology* **517**:3-8.
27. **Wulan WN, Heydet D, Walker EJ, Gahan ME, Ghildyal R.** 2015. Nucleocytoplasmic transport of nucleocapsid proteins of enveloped RNA viruses. *Front Microbiol* **6**:553.
28. **Takayama I, Sato H, Watanabe A, Omi-Furutani M, Sugai A, Kanki K, Yoneda M, Kai C.** 2012. The nucleocapsid protein of measles virus blocks host interferon response. *Virology* **424**(1):45-55.
29. **Wurm T, Chen H, Hodgson T, Britton P, Brooks G, Hiscox JA.** 2001. Localization to the nucleolus is a common feature of coronavirus nucleoproteins, and the protein may disrupt host cell division. *J Virol* **75**(19):9345-56.
30. **Gussow AB, Auslander N, Faure G, Wolf YI, Zhang F, Koonin EV.** 2020. Genomic determinants of pathogenicity in SARS-CoV-2 and other human coronaviruses. *Proc Natl Acad Sci U S A* **117**(26):15193-9.
31. **Cokol M, Nair R, Rost B.** 2000. Finding nuclear localization signals. *EMBO reports* **1**(5):411-5.
32. **Casari I, Manfredi M, Metharom P, Falasca M.** 2021. Dissecting lipid metabolism alterations in SARS-CoV-2. *Prog Lipid Res*:101092.
33. **Kroemer G, Mariño G, Levine B.** 2010. Autophagy and the integrated stress response. *Mol Cell* **40**(2):280-93.
34. **He C, Klionsky DJ.** 2009. Regulation mechanisms and signaling pathways of autophagy. *Annu Rev Genet* **43**:67-93.
35. **Garcia EJ, Vevea JD, Pon LA.** 2018. Lipid droplet autophagy during energy mobilization, lipid homeostasis and protein quality control. *Front Biosci* (Landmark Ed) **23**:1552-63.
36. **Jackson WT, Giddings Jr TH, Taylor MP, Mulinyawe S, Rabinovitch M, Kopito RR, Kirkegaard K.** 2005. Subversion of cellular autophagosomal machinery by RNA viruses. *PLoS Biol* **3**(5):e156.
37. **Dreux M, Gastaminza P, Wieland SF, Chisari FV.** 2009. The autophagy machinery is required to initiate hepatitis C virus replication. *Proc Natl Acad Sci U S A* **106**(33):14046-51.
38. **Cong Y, Verlhac P, Reggiori F.** 2017. The Interaction between Nidovirales and Autophagy Components. *Viruses* **9**(7).
39. **Gassen NC, Papies J, Bajaj T, Dethloff F, Emanuel J, Weckmann K, Heinz DE, Heinemann N, Lennarz M, Richter A, Niemeyer D.** 2020. Analysis of SARS-CoV-2-controlled autophagy reveals spermidine, MK-2206, and niclosamide as putative antiviral therapeutics. *bioRxiv*.
40. **Prentice E, Jerome WG, Yoshimori T, Mizushima N, Denison MR.** 2004. Coronavirus replication complex formation utilizes components of cellular autophagy. *J Biol Chem* **279**(11):10136-41.
41. **Yang CW, Peng TT, Hsu HY, Lee YZ, Wu SH, Lin WH, Ke YY, Hsu TA, Yeh TK, Huang WZ, Lin JH.** 2020. Repurposing old drugs as antiviral agents for coronaviruses. *Biomed J* **43**(4):368-74.
42. **Xu J, Shi PY, Li H, Zhou J.** 2020. Broad Spectrum Antiviral Agent Niclosamide and Its Therapeutic Potential. *ACS Infect Dis* **6**(5):909-15.
43. **Pino-de la Fuente F, Quezada L, Sepúlveda C, Monsalves-Alvarez M, Rodríguez JM, Sacristan C, Chiong M, Llanos M, Espinosa A, Troncoso R.** 2019. Exercise regulates lipid droplet dynamics in normal and fatty liver. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids* **1864**(12):158519.
44. **Greenberg AS, Coleman RA, Kraemer FB, McManaman JL, Obin MS, Puri V, Yan QW, Miyoshi H, Mashek DG.** 2011. The role of lipid droplets in metabolic disease in rodents and humans. *J Clin Invest* **121**(6):2102-10.
45. **Krahmer N, Farese RV, Walther TC.** Balancing the fat: lipid droplets and human disease. *EMBO Mol Med* **5**(7):973-83.
46. **Scheen AJ.** 2020. Statins and clinical outcomes with COVID-19: Meta-analyses of observational studies. *Diabetes Metab* **47**(6):101220.

47. **Targher G, Mantovani A, Wang XB, Yan HD, Sun QF, Pan KH, Byrne CD, Zheng KI, Chen YP, Eslam M, George J.** 2020. Patients with diabetes are at higher risk for severe illness from COVID-19. *Diabetes & Metabolism* **46**(4):335-7.
48. **Gluchowski NL, Becuwe M, Walther TC, Farese RV.** 2017. Lipid droplets and liver disease: from basic biology to clinical implications. *Nat Rev Gastroenterol Hepatol* **14**(6):343-55.
49. Özcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Özdelen E, Tuncman G, Görgün C, Glimcher LH, Hotamisligil GS. 2004. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* **306**(5695):457-61.
50. **Lee AH, Scapa EF, Cohen DE, Glimcher LH.** 2008. Regulation of hepatic lipogenesis by the transcription factor XBP1. *Science* **320**(5882):1492-6.
51. **Gregor MF, Hotamisligil GS.** 2011. Inflammatory mechanisms in obesity. *Annu Rev Immunol* **29**:415-45.
52. **Sunyer J, Jarvis D, Pekkanen J, Chinn S, Janson C, Leynaert B, Luczynska C, Garcia-Esteban R, Burney P, Antó JM.** 2004. Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. *J Allergy Clin Immunol* **114**(5):1033-9.
53. **Bousquet J, Anto JM, Iaccarino G, Czarlewski W, Haahtela T, Anto A, Akdis CA, Blain H, Canonica GW, Cardona V, Cruz AA.** 2020. Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clin Transl Allergy* **10**:16.
54. **Zhang J, Lan Y, Sanyal S.** 2017. Modulation of Lipid Droplet Metabolism-A Potential Target for Therapeutic Intervention in flaviviridae infections. *Front Microbiol* **8**:2286.
55. **Georgel P, Schuster C, Zeisel MB, Stoll-Keller F, Berg T, Bahram S, Baumert TF.** 2010. Virus-host interactions in hepatitis C virus infection: implications for molecular pathogenesis and antiviral strategies. *Trends Mol Med* **16**(6):277-86.