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Lipid balance remodelling by human positive-strand RNA viruses and the contribution of lysosomes

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ABSTRACT

A marked reorganization of internal membranes occurs in the cytoplasm of cells infected by single stranded positive-sense RNA viruses. Most cell compartments change their asset to provide lipids for membrane rearrangement into replication organelles, where to concentrate viral proteins and enzymes while hiding from pathogen pattern recognition molecules. Because the endoplasmic reticulum is a central hub for lipid metabolism, when viruses hijack the organelle to form their replication organelles, a cascade of events change the intracellular environment. This results in a marked increase in lipid consumption, both by lipolysis and lipophagy of lipid droplets. In addition, lipids are used to produce energy for viral replication. At the same time, inflammation is started by signalling lipids, where lysosomal processing plays a relevant role. This review is aimed at providing an overview on what takes place after human class IV viruses have released their genome into the host cell and the consequences on lipid metabolism, including lysosomes.

1. Introduction

Lipids are constitutive molecules of cell membranes, but they are also involved in signalling in all cell types, as well as in energy supply. Thousands of lipid species make up the lipid universe in cells. [https://www.lipidmaps.org/]. They are synthesized *de novo* and/or transformed during membrane remodelling in a delicate balance that contributes to regulate a variety of vital functions in cells. For this reason, their homeostasis is one of the most complicated pathways in cell metabolism, being finely regulated by an enormous number of factors that are located in every subcellular compartment (Yoon et al., 2021). Most cells mainly uptake exogenous lipids: briefly, to enter cells, free fatty acids (FAs), and triglycerides (TGs) are captured from the bloodstream by specific receptors, such as the fatty acid translocase CD36, and other membrane proteins. Once inside, they may be β-oxidized by mitochondria or peroxisomes to provide energy. Specific very long-chain FAs are oxidized in peroxisomes, whereas excess FAs, that would be toxic if free in the cytoplasm, are turned into TGs and stored in lipid droplets (LDs). These increasingly studied organelles are key in lipid homeostasis, as discussed below.

Bioactive lipids include acylglycerol species, lysophospholipids, sphingolipids, and cholesterol metabolites, to name but few. These are not only products of lipid metabolism, but also important signalling molecules in tissue homeostasis and pathology, including viral infection (Yoon et al., 2021). Because the same lipid mediators might exert various functions by acting on different receptors, it is crucial to clarify the signal transduction mechanism for every bioactive lipid, in order to comprehend their impact on viral replication.

Recently, viral modulation of lipid metabolism during infection has been the focus of considerable scientific effort. Indeed, lipids are crucial for efficient viral entry, replication and release (Ketter and Randall, 2019). Once they have entered cells, viruses need to provide for viral production, while avoiding autophagic digestion and intrinsic cell defences. Single-stranded positive sense RNA viruses (ss + V) generate membranous replication organelles (ROs) where to replicate efficiently.

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Abbreviations

acylglycerolphosphate acyltransferase AGPAT
adipose trygliceride lipase ATGL, aka PNPLA2
5′ adenosine-monophosphate activated kinase AMPK
Autophagy-related protein ATG
Bactericidal/permeability-increasing protein fold-containing family B member 3 BPIFB3
ceramide CE
Comparative Gene Identification-58 CGI-58
Coxsackie virus CV
Cyclic AMP-dependent transcription factor ATF-6 α ATF6
Cyclooxygenase COX
cytosolic phospholipase-A2α cPLA2α
Dengue virus DENV
diacylglycerol-acyltransferase DGAT
double membrane vesicles DMV
endoplasmic reticulum ER
Fatty acid FA
Fatty acid synthase FASN
hepatitis C virus HCV
inositol-requiring protein-1 IRE1
Interferon IFN
light chain 3 LC3-II
lipid droplet LD
lysophospholipid LPL
microtubule-associated protein 1 light chain 3 LC3-II
non-structural NS
non-structural protein NSP
NAE-hydrolyzing acid amidase NAAA
N-acylethanolamine NAE
Perilipin PLIN
phosphatidylinositol PI
phosphatidylinositol (4,5)-bisphosphate PIP2
phosphatidylinositol (3,4,5)-trisphosphate PIP3
phosphatidylinositol 3-kinase PI3K
phospholipase PLA
Peroxisome proliferator-Activated Receptor PPAR
Protein kinase RNA-like ER kinase PERK
replicating organelle RO
Reticulophagy regulator 1 RETREG1
single stranded positive-sense RNA virus ss + V
site 1- protease S1P
site 2- protease S2P
sphingomyelin SM
sphingosine kinase SK
sphingosine-1-phosphate Sp1P
sterol regulatory element-binding protein 1 SREBP-1
Transmembrane protein 41B TMEM41B
Triglyceride TG
unfolded protein response UPR
Vacuole Membrane Protein 1 VMP1
West Nile virus WNV
Zika virus ZIKV

While doing so, they upset the whole lipid balance in cells, leading to the production of structural and bioactive lipids, that in turn bring along downstream effects.

Drug repurposing is a rapid way of using drugs off-label, without having to perform phase I and II clinical trials again. Because lipid balance is also altered in cancerous cells, many clinical trials are aimed at testing drugs targeting lipid metabolism to design novel anticancer agents (Ogretmen, 2017). These may be used as antivirals, once their targets are pinpointed as relevant ones for viral replication. Thus, identification of relevant pathways for each virus is decisive because different viral replication cycles may be oppositely influenced by defined therapeutic approaches, (Dissanayake et al., 2021). In this review, we have designed each Section to touch upon the physiological role of each organelle. Next, we highlighted how ss + V alter their physiology while assembling their progeny. Lastly, we pinpointed molecules where therapeutic agents could be targeted or repurposed within the pathways described. Finally, we highlight what takes place in lysosomes, as relatively novel targets of antiviral therapy (Table 1).

2. The endoplasmic reticulum, the mother of all membranes

The endoplasmic reticulum (ER) is the largest subcellular membranous organelle, the many functions of which account for its complex architecture. The ER is also the site where glycoproteins are synthesized, folded and glycosylated (Schwarz and Blower, 2016). Nascent proteins are targeted to the ER by the first stretch of amino acids translated, the signal peptide; the rest of the translated protein then accumulates into the lumen of the rough ER, where it is subsequently folded and/or modified.

The ER is composed of a continuous membrane including the nuclear envelope, flat and stacked sheets and branched tubules, that dynamically change to comply with cellular needs and functions. Integral, resident proteins regulate shape, size and function of the different subcompartments (Schwarz and Blower, 2016). The ER is therefore the major site of lipid metabolism for the synthesis of sterols and phospholipids for all biological membranes. Importantly, the enzymes for the synthesis of eicosanoid lipids may be found in the ER.

Several cellular factors have been implicated in membrane expansion and remodelling. Sheet formation requires factors, such as Rab10, that are more abundant at ER membrane fusion sites (Shibata et al., 2010). To promote tubule formation, reticulon proteins, like RTN3.1A, are found in highly curved areas of the ER, interacting with DP1/Yop1/REEP5-6 and REEP1-4 family members, to stabilize curvature (Hu et al., 2009). Flaviviridae, including the arthropod-borne genus *Flavivirus* and the hepatitis C virus (HCV) genus *Hepacivirus*, depend on membrane reorganization for every step of their replication. Their entire intracellular life cycle occurs in close association to the ER, where translation of the viral polyprotein takes place (Barnard et al., 2021). All Flaviviruses encode non-structural (NS) proteins NS4A and B, that have a relevant role in the formation of ROs. As an example, West Nile virus (WNV) NS4A and B were shown to guide the redistribution of RTN3.1 to bend membranes in RO formation (Aktepe et al., 2017). Membrane remodelling requires degradation and new synthesis/recruitment of lipids. Degradation of excess ER membrane is mediated by pivotal molecules, like the recently described reticulophagy regulator 1 (RETREG1, aka FAM134B), belonging to an ER-anchored autophagy receptor family. RETREG1 targets ER membrane fragments into autophagosomes *via* the autophagy-related protein-8 (Khaminets et al., 2015; Reggio et al., 2021). This process is downregulated by specific proteins, like Bactericidal/permeability-increasing protein fold-containing family B member 3 (BPIFB3), which acts by inhibiting RETREG-1 (Delorme-Axford et al., 2014). Building blocks for new membranes are provided by cytoplasmic FA synthase (FASN), an enzymatic system that, in concert with other enzymes, catalyses the synthesis of FAs, mostly the long-chain saturated FA palmitate (Yoon et al., 2021). Processing of FAs to TGs is carried out by ER-resident enzymes, mainly diacylglycerol-acyltransferase (DGAT) −1 and −2. FASN is transcriptionally upregulated by sterol regulatory element-binding protein (SREBP)-1 (Fig. 1). This factor has been recently proven to be a key factor in the replication of a wide variety of viruses, including

Table 1
Lipid metabolism molecules that can be targeted by repurposing existing drugs as antiviral agents.

Target molecule	Activity in viral replication	Examples of possible drugs	Action described (disease treated)	Drug status (ID clinical trial)	Virus(es) possibly inhibited	Reference
Acid ceramidase	hydrolyses ceramides	ceranib-2	Anticancer	in vitro	Measles virus (might enhance HSV 1)	Grafen et al. (2019) (Lang et al., 2020a,b) Vethakanraj et al. (2018)
AGPAT	RO formation	FSG67	Reduces body weight; increases insulin sensitivity	Mouse model	HCV SARS-CoV-2	Wydysh et al. (2009) Kuhajda et al. (2011) Yu et al. (2018)
ATGL	Viral assembly, arachidonic acid release, inflammation	Atglistatin	Insulin resistance, obesity, Liver steatosis	Mouse model (not for humans)	HCV	(Schweiger et al., 2017; Vieyres et al., 2020)
ATF6	UPR membrane remodelling	4-phenyl-butyric acid	Urea cycle disorders	FDA approved	WNV, Tick borne encephalitis virus	(Ambrose and Mackenzie, 2013; Chipurupalli et al., 2022; Yu et al., 2013; Zhang et al., 2013)
BPIFB3 (aka FAM134B)	Inhibition of autophagy	vitexin	Breast cancer,	in vitro	Coxsackie (replicate when target inactive) Flaviviridae (replicate when target active)	Chipurupalli et al. (2022)
CD36	FA intake	AP5055, AP5258	Diabetic dyslipidemia, atherosclerosis	In vitro	Hepatitis B virus	(Geloen et al., 2012; Huang et al., 2017)
CE synthase and desaturase	CE biosynthesis	Fenretinide (CE desaturase inhibitor) Fumonisin B1 (CE synthase 1 inhibitor) **P053**	Inflammation, Cancer	Phase 4 Clinical trial (NCT01553071)	ZIKV, WNV, Rhinoviruses, Coronaviruses (might enhance DENV and others)	(Aktepe et al., 2015; Beckmann and Becker, 2021; Finnegan and Blumenthal, 2006; Pitts et al., 2017; Skácel et al., 2021)
cPLA2α	RO genesis, synthesis eicosanoids and lysophospholipids, inflammation,	AVX420, AVX002 AVX001 pyrrophenone	Multiple mieloma Psoriasis Inhibition of Ca++ release	In vitro Phase 1/2a clinical trial (NCT05164393) In vitro	Coronaviridae	Ashcroft et al. (2020) (Yun et al., 2016)
DGAT	LD formation	ISIS 484137	Inhibition of DGAT2, treatment of Hepatic steatosis,	Phase 2 trial (NCT03334214)	Flaviviridae, Coronaviridae	(Alketbi et al., 2021; Camus et al., 2013; da Silva Gomes Dias et al., 2020; Fonnesu et al., 2022; Nardi et al., 2019)
FASN	FA synthesis, viral entry	ACSS2, FT113, TVB2640, GSK-214069, TVB3664, FASN–IN–4	Solid tumors, non-alcoholic steatosis	In vitro	DENV, SARS-CoV-2	(Jordan and Randall, 2017; Liu et al., 2021)
		TVB-2640		Phase 2 trial		(Aliyari et al., 2022; Chu et al., 2021)
		orlistat	obesity	FDA-approved	DENV, ZIKV, Chikungunya virus,	(Hitakarun et al., 2020; Loomba et al., 2021)
IRE1	Glycoprotein accumulation. Membrane formation	6-thioguanine STF-083010	leukemia, inflammatory bowel disease counteracts inflammation, alleviates atherosclerosis	FDA-approved,	Influenza A viruses ZIKV	Slaine et al. (2021) (Huang et al., 2020; Raymundo et al., 2020; Yang et al., 2020)
NAAA	Ethanolamine hydrolysis (LD downregulation)	Atractylodin	Counteracts LPS-Induced Microglial Activation	Tested in vitro	ZIKV, SARS-CoV-2	Yang et al. (2020)
		ARN077, ARN726	Anti-inflammatory and viral replication	Tested in vitro	ZIKV, SARS-CoV-2	(Lai et al., submitted)
PI3K	LD formation	Idelalisib, BKM120, BYL719	Chronic lymphocitic leukemia Cancer treatment	licensed Phase 2 clinical trial (NCT04342117)	ZIKV DENV SARS-CoV-2	Monson et al. (2021)a,b
PLIN1	LD formation	4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside	Treatment of obesity	In silico	ZIKV DENV SARS-CoV-2	Noureldein (2014)
		Apelin-13	Promotes lipolysis reduces LD numbers			(Wang et al., 2021)
PLIN2		None found			HCV	

(*continued on next page*)

Table 1 (*continued*)

Target molecule	Activity in viral replication	Examples of possible drugs	Action described (disease treated)	Drug status (ID clinical trial)	Virus(es) possibly inhibited	Reference
	LD size, Inflammation, lipoprotein production in macrophages					(Ferguson et al., 2017; Huang et al., 2019; Lassen et al., 2019)
PPARα	Peroxisome genesis, FA oxidation, antiinflammatory	PEA (agonist)	antiinflammatory	Available over the counter	ZIKV, SARS-CoV-2 (replicate when active)	Fonnesu et al. (2022)
PPARγ	Stimulates lipid uptake (macrophages)	Pioglitazone (agonist) T0070907 (antagonist)	Type 2 diabetes Bladder Cancer	Phase 4 clinical trial (NCT04535700)	HIV CMV	(Layrolle et al., 2021; Lv et al., 2019)
RAB7	Endosomal trafficking	CID 1067700	Murine lupus	Mouse model	Coronaviridae	(Agola et al., 2012; Cao et al., 2018; Ghosh et al., 2020; Lam et al., 2016)
SK1	Lysosomal Sp1P production, inflammation	SK1–I	Glioblastoma, HCC	Phase 2 clinical trial (NCT02939807)	WNV, HCV	(Aktepe et al., 2015; Gewaid et al., 2020) Cao et al. (2018)
SMase (acid)	Lysosomal CE production, inflammation	FIASMAs class, ARC39	Depression, Cystic fibrosis, Cancer, Atherosclerosis, many others	Many licensed In vitro	SARS-CoV-2	(Loas and le Corre, 2021; Naser et al., 2020) (Loas and le Corre, 2021)
SREBP-1	Upregulation of PPARγ and CD36, Transcription of FASN	betulin	hepatocellular carcinoma		HCV, SARS-CoV-2	(Da Silva et al., 2020; Yin et al., 2019)
TMEM41B	RO formation	None found			Flaviviruses SARS-CoV-2 Coronaviridae	(Hoffmann et al., 2021; Huang et al., 2021; Trimarco et al., 2021)
VSP34	Upregulates recycling endosomal cargoes	SAR405	alters vesicle trafficking and autophagy; anticancer		Flaviviruses SARS-CoV-2	(Giridharan et al., 2022; Hoffmann et al., 2021; Hu et al., 2021; Ronan et al., 2014)

SARS-CoV-2, and a potential target for broad antiviral activity (Yuan et al., 2019).

Given the close association of Flaviviral replication with the ER, it is not surprising that BPIFB3, as a major activator of ER expansion, is hijacked for efficient dengue virus (DENV) and Zika virus (ZIKV) infection. BPIFB3 depletion can restrict infection in the early stages of replication by enhancing specifically RETREG1-mediated reticulophagy, independently of innate immune activation (Evans et al., 2020). Both ZIKV and DENV inhibit ER degradation by cleaving RETREG1, thus allowing an accumulation of ER membranes (Lennemann and Coyne, 2017). In addition, FASN is recruited to sites of RO formation by the DENV protease NS3 to provide lipids (Heaton et al., 2010).

2.1. The unfolded protein response: a double-edged sword

High concentrations of un- or mis-folded protein, dead cell debris and ER stress in general cause the ER to turn on a reaction, called the unfolded protein response (UPR) (Ron and Walter, 2007). Accumulation of large quantities of protein, nucleic acid, and cell debris are hallmarks of viral infection, which is consequently a major cause of ER stress. To proceed with their replication, viruses must deal with the UPR and quite often they try to do so by deviating this dynamic process to their advantage.

The UPR response is aimed at relieving ER overload by 1) expanding the ER to comply with increased demand of work; 2) reducing protein translation and ER-associated protein degradation and increasing secretory capacity to diminish protein load in the ER; 3) activating autophagy to eliminate large vesicular cargos. The UPR also turns on lipolysis, inflammation and apoptosis, as discussed below. All starts by sensing ER luminal stress leading to activation of specific genes. To this aim, three different classes of independent but communicating ER stress sensors operate distinct arms of the UPR:

1) inositol-requiring protein-1 (IRE1) amplifies stress response *via* XBP1. It is one of the key sensors starting UPR, is a transmembrane protein kinase and endoribonuclease(Riaz et al., 2020). It mediates splicing of X-box Binding Protein 1 (XBP1) mRNA, a transcription factor involved in upregulating additional stress response genes. These encode proteins involved in phospholipid synthesis and provide building blocks for endomembrane proliferation. The IRE1/XBP1 pathway was identified as a critical regulator of liver lipid metabolism and of eicosanoid synthesis (Hammock et al., 2020). Interestingly, IRE1 is activated by ZIKV to promote its own replication, giving rise to accumulation of monounsaturated FAs and upregulation of enzymes involved in FA metabolism, such as stearoyl coenzyme A desaturase 1, ultimately leading to LD production (Huang et al., 2020). Thus, IRE1 inhibitors may suppress ZIKV replication.
2) Cyclic AMP-dependent transcription factor ATF-6 α (ATF6) also amplifies stress response. Activated ATF6 is transported from the ER to the Golgi apparatus, where it is cleaved by Golgi-resident proteases site 1- and site 2- protease (S1P and S2P, *aka* subtilisin). Once cleaved, ATF6 promotes transcriptional output in the nucleus (Almanza et al., 2019). Several Picornaviral species activate this signalling cascade to initiate autophagy (Song et al., 2022; Wu et al., 2021). Interestingly, ATF6 is also activated by specific signalling sphingolipids (dihydrosphingosine and dihydroceramides) and is an important actor during lipotoxicity (Tam et al., 2018). Of note, S1P and S2P are key players in lipid balance; for example, during sterol depletion, the SREBP precursor is also transported to the Golgi apparatus, where it is cleaved by S1P and S2P (Danyukova et al., 2022).
3) Protein kinase RNA (PKR)-like ER kinase (PERK) diminishes ER protein content. Activation of PERK leads to eIF2 phosphorylation and consequent reduction of protein synthesis. Signals of apoptosis and autophagy induced by ER stress are transduced through the

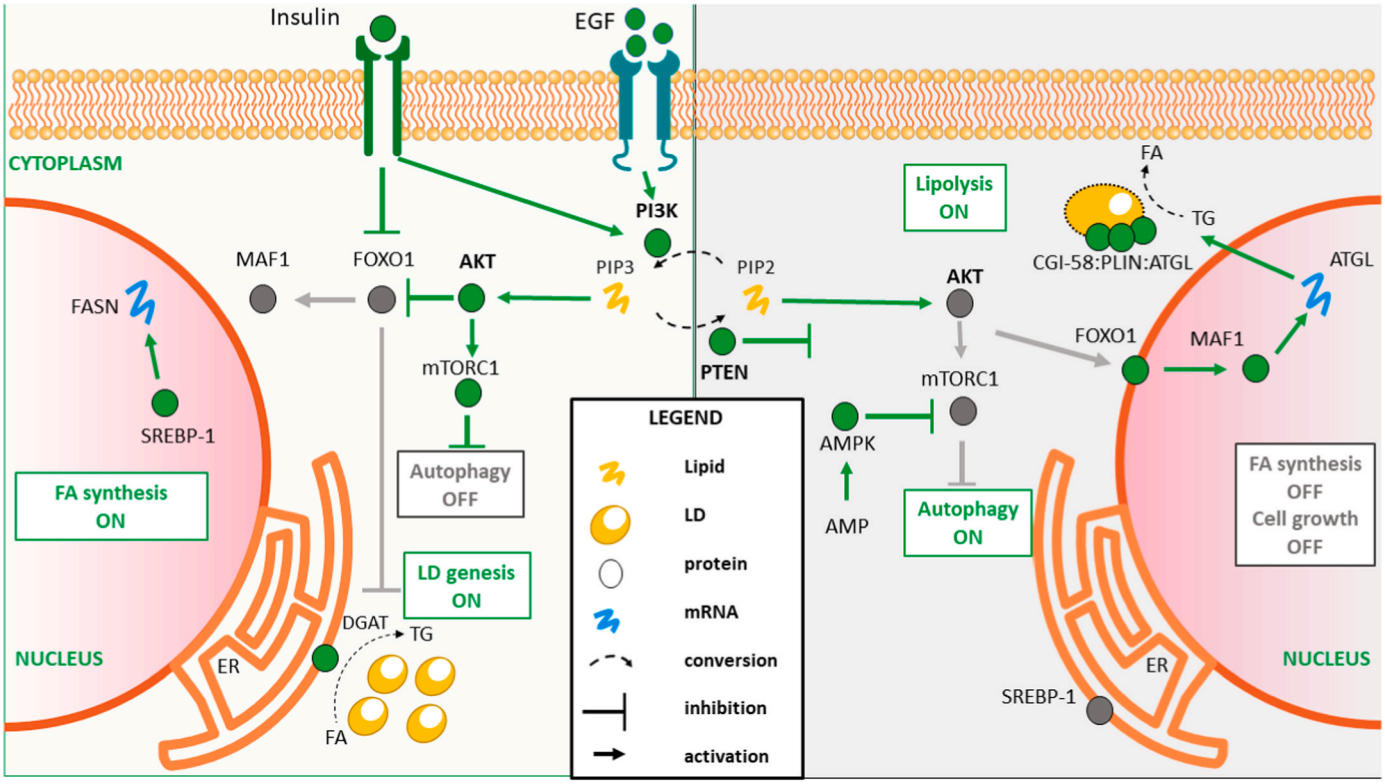

Fig. 1. A synthetic view of the PI3K/PTEN pathway, as addressed in this review.
The balance between PIP2 and PIP3 is crucial in AKT signalling and is kept by PI3K, building up PIP3, and PTEN, that dephosphorylates PIP3 to PIP2.
LEFT PANEL: PI3K is activated, e.g. by EGF and insulin when nutrients are available, to promote transcription of FASN and activation of SREBP, leading to lipid synthesis and LD formation. PI3K causes accumulation of PIP3, in turn activating AKT by phosphorylation. AKT turns on lipid metabolism *via* blockage of FOXO1/MAF1. When AKT is active, mTORC1 is activated, inhibiting autophagy.
RIGHT PANEL: FOXO1/MAF1 normally favour lipid usage by enhancing transcription of ATGL and preventing FASN transcription (right panel). Autophagy is active because mTORC1 is inhibited. LDs are used by lipophagy and lipolysis. Green: active, grey: not active. For abbreviations see list.

PERK pathway to trigger cell death or maintain cell survival. Indeed, PERK might act as a switching mechanism between autophagy and apoptosis (Almanza et al., 2019; Raines et al., 2022).

2.2. Double membrane vesicles and lipid balance

Extensive membrane remodelling occurs in the ER during autophagy, a recycling process that breaks down cellular components during nutrient starvation and has been found to be essential in the regulation of lipid content in cells (Singh et al., 2009). As mentioned above, autophagy can be also activated by the UPR and can be envisioned as part of the cell reaction to infection, in addition to being an important pathway in TG breakdown (Choi et al., 2018). Macroautophagy (referred to as autophagy) starts when autophagy-related proteins (ATGs), like ATG-5 and -7, microtubule-associated protein 1 light chain 3 (LC3-II), as well as others, begin double membrane vesicle (DMV) generation, starting from the induction of curvature in the membrane, proceeding with phagophore generation and ending with autophagosome pinching off. Phosphatidic acid, a lipid produced by acyl glycerol phosphate acyltransferase (AGPAT)-1 and −2 in the ER, is required for membrane curvature (Tanguy et al., 2019). Rab7, belonging to the Rab protein family, is found to decorate autophagosomes as a major player in targeting autophagosomes to lysosomes for cargo degradation (Cantalupo et al., 2001). Autophagosomes may engulf LDs similarly to other cargos; this process is called lipophagy, whereby neutral lipids contained in LDs are hydrolyzed by lysosomal lipases. Because autophagy is essential to LD usage, by modulating it during RO formation, viruses also modulate lipid storage and breakdown (Singh et al., 2009).

FAs resulting from lipophagy may be β-oxidized as a source of fuel by mitochondria, but also in peroxisomes (Singh et al., 2009). Peroxisomes and mitochondria play key roles in inflammation and immunity; therefore, they deserve more attention than can be accommodated within the scope of this review. For further details, we refer the reader to very recent work (Cook et al., 2019; Foo et al., 2022). Briefly, mitochondria are, in first place, devoted to energy production in sync with FA oxidation, whereby ATP is synthesized. Second, they are involved in production of reactive oxygen species during inflammation. Third, they are also pivotal in intrinsic cell immunity, where the mitochondrial anti-viral signaling (MAVS) pathway modulates IFN type I response. Fourth, they respond to Ca++ release during UPR by promoting apoptosis. Because these are critical functions, viruses must interact with mitochondria, by steering their apoptotic function and in other ways. Peroxisomes can be generated *ex novo* from the ER and mitochondria, under the control of Peroxisome Proliferator-Activated Receptor (PPAR) α, a member of a family of nuclear transcription factors activated by specific lipids, but also by fission of pre-existing peroxisomes. They were discovered as immune signalling organelles, where MAVS can also be found, but many other functions of theirs were discovered successively. Among these, synthesis of reactive oxygen species coupled to β-oxidation, especially of very-long-chain FAs, is regulated by PPAR transcription factors (Lange et al., 2022) (Fig. 2), These organelles are often targets of specific viral proteins that aim at neutralizing their action, rather than exploiting them for replication. As an example, the Japanese encephalitis virus downregulates PPAR signalling and FA metabolism in human dendritic cells, leading to virus-favourable dendritic cell maturation and antiviral responses (Chauhan et al., 2021).

Autophagy can be envisioned as an antiviral process, aimed at

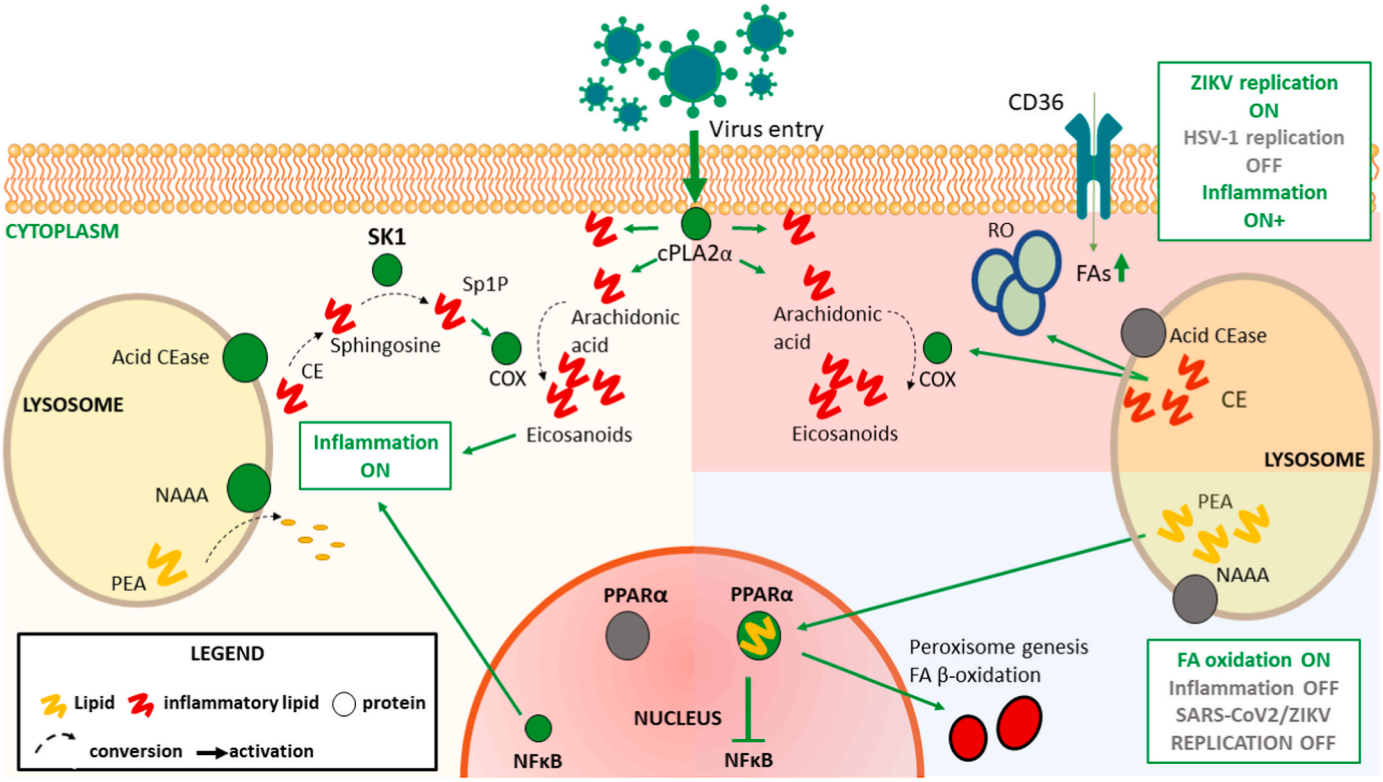

Fig. 2. An overview of the consequences of lysosome enzyme activity or blockage during viral infection and inflammation. Entry of viruses causes build up of LDs, for example by cPLA2a and, in sync, to form arachidonic acid and LPLs. Arachidonic acid is converted to inflammatory mediators by COX, which is activated by high concentrations of CEs. In the lysosome, NAAA degrades PEA and other NAEs, thereby hindering PPARα activation and lipolysis. In addition, SMase converts SM to CEs. Acid Cease uses CEs to produce sphingosine, that is phosphorylated to Sp1P by SKs in the cytoplasm. Inflammation is active (left panel, pink background). When acid Cease is blocked by drugs, inflammation is exacerbated, and ZIKV replication enhanced. The contribution of the accumulation of CEs in inflammation and RO generation is highlighted (upper right, red background). In contrast, when NAAA is blocked, inflammation is quenched by activation of PPARα and inactivation of NFκB. Consequently, SARS-CoV-2 replication is quenched (lower right, light blue background). Green circles represent active proteins and effects, inactive ones are in grey. For abbreviations, see list.

keeping cellular homeostasis, including lipid balance (Choi et al., 2018). However, ss + V families of the Togaviridae, Coronaviridae, Flaviviridae and even Picornaviridae, a family of naked viruses, profit from it by modifying membranes belonging to the secretory/autophagic pathway to produce ROs in infected cells. Although viruses tend to save on genetic material, many encode NS proteins that have at least one activity devoted to build ROs, proving how important they are to viral life (Paul, 2013; Wolff et al., 2020). To this aim, several viral NS proteins sequester host factors normally regulating membrane scaffolding or acting during autophagy and/or secretion.

The role of autophagy in viral replication is particularly evident in Flaviviral replication cycle, both in their human and arthropod host (Brackney et al., 2020). In addition, SARS-CoV-2, MERS CoV and the mouse hepatitis virus, belonging to the family of enveloped ss + Vs *Coronaviridae*, replicate in a way that is reminiscent of *Flaviridae*, in that they rely on the ER in many, if not all, steps; they also exploit autophagy. The way these viruses usurp autophagy varies substantially: some species, like HCV, and SARS-CoV-2, will cause phosphatidic acid accumulation with a striking similarity to what occurs during early autophagy, whereas others like ZIKV and DENV, will cause invaginations of the ER, independently from phosphatidic acid (Tabata et al., 2021). In this respect, inhibition of AGPAT may be envisioned as a relatively specific target for anti-HCV and SARS-CoV-2 therapy (Table 1).

Membrane contact between different organelles, like ER, LDs, mitochondria and peroxisomes, is made to transfer ions, lipids and proteins. To preserve membrane identity or, alternatively, to cause fusion, membrane lipid rearrangement occurs at contact sites; to this aim, resident proteins tether organelles to keep membranes distinct (Scorrano et al., 2019). At contact sites, specific proteins are enriched depending on the function of the contact, whereas non-resident proteins can be either recruited or repelled. Transmembrane protein 41B (TMEM41B), for instance, is an ER-resident phospholipid scramblase involved in lipid homeostasis and membrane dynamics processes (Hama et al., 2022). It participates in early phases of autophagy by recruiting lipids to assemble autophagosomes (Huang et al., 2021). Several properties of TMEM41B are shared by another autophagy-related ER protein, the Vacuole Membrane Protein 1 (VMP1), but this one also regulates contacts between LDs, mitochondria and endosomes (Zhao et al., 2017). Upon viral infection, VMP1 promotes formation of cytoplasmic vacuoles followed by cell death. Flaviviral NS4A and B have recently been found to hijack TMEM41B in human, mosquito and tick cells (Hoffmann et al., 2021). During translation of the viral polyprotein, TMEM41B associates with NS4A and NS4B to facilitate membrane curvature necessary for RO formation, after interaction with VMP1. Accordingly, WNV NS4A contributes to remodelling ER membranes by recruiting both viral and host proteins to cholesterol-rich microdomains within the ER, again facilitating RO formation (Mikulasova et al., 2021). For this reason, TMEM41B, but also NS4A and B, may be considered as candidates for indirect and direct, respectively, antiflaviviral drugs to inhibit the replication of a broad range of emerging and re-emerging Flaviviral pathogens.

Interestingly, TMEM14B was also found to be involved in SARS-CoV-2 replication (Hoffmann et al., 2021), in agreement with the observation that Coronaviruses strongly rely on remodelling host intracellular membranes to create their ROs (Wolff et al., 2020).

Very recent results by Ghosh et al. highlight that even the very final

stages of autophagy may be a possible target for therapy of different classes of viruses (Ghosh et al., 2020). They show that Rab7 is essential for mouse hepatitis virus and SARS-CoV-2 egress from cells by the exocytic pathway, and not the biosynthetic secretory pathway as had been assumed. SARS-CoV-2, and MERS, inhibit the activity of Rab7, thereby hindering lysosome/autophagosome fusion and acidification. Interestingly, Influenza virus, with a completely different replication cycle, has also been demonstrated to evade autophagy by blocking Rab7-mediated lysosomal degradation *via* its multifunctional structural protein M2 (Martin-Sancho et al., 2021). Moreover, Williams et al. demonstrated that VPS34, a phosphatidylinositol (PI)-3-kinase (PI3K) that positively regulates the recycling of endosomal cargoes (Giridharan et al., 2022), is used to make membranes available for RO formation during SARS-CoV-2 infection and may be another drug target to suppress viral replication (Williams et al., 2021).

Picornaviruses are small, non-enveloped ss + V; the genus *Enterovirus* contains important human pathogens, poliovirus to name but one. Differently from Corona- and Flavi-viral ROs, Enteroviral ROs are made by single membrane tubules in the earlier stages of infection, which are then turned into DMVs as infection proceeds (Paul, 2013; Wolff et al., 2020). During *Enterovirus* infection, the autophagy pathway provides membranous scaffolds for generation of ROs, where Golgi proteins and the autophagy marker LC3-II are found to be sequestered. In a late stage of the replication cycle, DMVs form multilamellar vesicles in the cytoplasm. The biogenesis of these ROs seems to involve first ER membranes and then the Golgi membranes (Melia et al., 2019; van der Schaar et al., 2016). Enteroviral 2C and 2B proteins tether the LDs to the ROs promoting the transfer of FAs from LDs to ROs. Indeed, when the lipidic flux from LDs to ROs is blocked by pharmacological inhibition, ROs are disrupted and viral replication is impaired (Laufman et al., 2019; Melia et al., 2019). Coxsackie virus (CV)–B3 infection causes the inhibition of autophagosome-autolysosome fusion through CV-B3 proteinase 3C, which cleaves two proteins vital for autophagosome fusion, TFEB and TRAF6. This induces accumulation of autophagosomes, providing additional membranes for RO generation (Li et al., 2020; McPhail et al., 2020). Several host proteins are involved in Enteroviral RO biogenesis, the majority of which function in vesicular membrane traffic and non-vesicular lipid transfer. Upon enteroviral infection, RO formation requires phosphatidylinositol 4-Kinase β to phosphorylate PI to its phosphoinositide PI-4-phosphate (PI4P), highly represented in human cellular membranes. PI4P is suggested to be involved in the assembly of RNA polymerase complex and in cellular lipid rearrangement through the recruitment of cholesterol to ROs, modulating their fluidity and stability (McPhail et al., 2020). Importantly, phosphoinositide pool regulation by interconversion to differently phosphorylated PI compounds, most notably PI (4,5)-bisphosphate (PIP2) and PI (3,4,5)-trisphosphate (PIP3), is a crucial pathway of interconversion regulating membrane curvature but also the assembly of multiprotein complexes, phagocytosis, exocytosis, and cytoskeletal organization, and above all, lipid metabolism (Fig. 1) (Czech, 2000).

In addition to serving as a scaffold for the replication of the poliovirus genome of, the latter may use autophagy for the non-lytic release of progeny, as depletion of autophagy genes was found to have a more significant effect on extracellular viral release than on viral replication (Choi et al., 2018). This might be connected to the fact that accumulation of LDs resulting from inhibition of lipophagy exerts a toxic/lytic effect (Singh et al., 2009).

Lipophagy is involved also in Flaviviral encapsidation: to use the energy stored in LDs, DENV post-transcriptionally downregulates the lipid phosphatase activity of PTEN, thereby allowing FOXO1/Maf1 signalling and triggering lipophagy, and FASN (Fig. 1), with a beneficial effect on viral replication Consequently, pharmacological inhibition of FASN might significantly impair DENV replication (Jordan and Randall, 2017; Liu et al., 2021). To stimulate lipophagy, DENV also activates 5′ adenosine-monophosphate activated kinase (AMPK) *via* phosphorylation by several upstream kinases. Activation of AMPK, a key energy-kinase sensing low levels of ATP activating autophagy and playing a role in regulating cellular energy metabolism, results in the inactivation of the autophagy suppressor mTORC1 (Fig. 1). AMPK is required for both induction of autophagosomes and the consumption of LD stores by DENV-induced lipophagy (Jordan and Randall, 2017). Thus, treatment with AMPK inhibitors, like dorsomorphin, can prevent DENV production, highlighting another possible target for therapy.

3. The expanding role of LDs in viral infection

LDs are ubiquitous and highly dynamic organelles enclosed by a phospholipid membrane monolayer containing neutral lipids, primarily TGs and cholesteryl esters. They are normally generated by processing of FAs to TGs by DGAT1 and DGAT2. LDs bud from the ER and retain DGAT-1 and -2, and adipose triglyceride lipase (ATGL, *aka* PNPLA2), on their surface, thus regulating their own size (Fig. 2) (Yoon et al., 2021). In addition to their major function in lipid storage and metabolism, LDs seem to have a number of newly found other functions (Monson et al., 2021a,b). The surface of LDs is also the site of dynamic recruitment of several other proteins that guide their size and contact with other organelles. Of these proteins, perilipins (PLIN) are the main regulators of LD genesis and breakdown (Monson et al., 2021a,b). PLINs work by inhibiting or favouring association of Comparative Gene Identification-58 (CGI-58) to ATGL, whereas removal of PLIN2 and PLIN3 from LD surface initiates lipophagy (Jaishy and Abel, 2016). Based on energy demand, a process called lipolysis allows cells to hydrolyse TGs in LDs back to FAs (Grabner et al., 2021). This process is carried out by lipases on the LD surface, mainly by ATGL (Fig. 1). Cells are normally able to regulate it at the transcriptional (by enhancing its expression *via* PPAR-γ and FOXO1 transcription factors) or CGI-58-mediated post-translational levels (Fig. 1), as well as by regulation of important enzymatic cofactors (Grabner et al., 2021).

LDs are found increased in number and size during attack by parasites, including viruses (Monson et al., 2021a,b). This is not a hallmark of ss + V infection, since other viruses like Rotaviruses have also been reported to modulate LD content quite some time ago (Cheung et al., 2010). They are upregulated even during infection by viruses as different as herpes and rabies virus (Monson et al., 2021a,b; Zhao et al., 2022). During infection, LD numbers are initially upregulated both by intrinsic cell defenses, turning on Toll-like receptor signalling and Interferon (IFN) type I and III responses, and specific virus-related IFN-independent mechanisms (Monson et al., 2021a,b). Early in infection by both ZIKV and herpes symplex-1 virus, LDs seem to increase in numbers by an alternative mechanism, that has also been identified in certain kinds of tumors; this involves the epidermal growth factor receptor and subsequent activation of PI-3-kinase (PI3K)/mTORC1 pathway (Fig. 1) (Monson et al., 2021a,b). Later in infection, another wave of LD increase is due to IFN-γ, highlighting that a bystander effect occurs in uninfected cells as well (Monson et al., 2021a,b). Interestingly, immune regulatory proteins may also be recruited on LDs, as shown for virus inhibitory protein, ER-associated, IFN inducible (Viperin), that increases IFN production when located to LDs (Bai et al., 2019). This suggests that another function of LDs is to cooperate with the ER in the synthesis of pro-inflammatory molecules, such as eicosanoids (Monson et al., 2021a,b). DENV and ZIKV use LDs as platforms for their assembly: an in vitro model recently showed that capsid-RNA complexes of DENV and ZIKV directly bound the ER membrane, possibly starting the process of virion assembly at the LD/ER interface (Ambroggio et al., 2021).

More recently, increases in LD numbers were reported also for SARS-CoV-2-infected cells. Like Flaviviridae, Coronaviridae seem to exploit LDs as scaffolds for virus replication and assembly. The importance of LDs in SARS-CoV-2 replication was confirmed by the observation that these organelles accumulate in SARS-CoV-2-infected monocytes and in type II pneumocytes from patients (Da Silva et al., 2020; Nardacci et al., 2021). In agreement with these observations, we also recently observed that SARS-CoV-2 replication can be repressed by disrupting LDs by

palmitoylethanolamide (PEA) treatment, discussed in Section 4. PEA blocks inflammation by activating PPAR-α, steering β-oxidation (Fig. 2) (Fonnesu et al., 2022; Yu et al., 2005).

As a mechanism to increase LDs, interaction between the DFCP1 (*aka* ZFYVE1) ER-resident protein, the LD tethering protein Rab18 and SARS-CoV-2 nonstructural protein (NSP) 7 was described (Li et al., 2019). Rab18 is required for LD growth and maturation from the ER (Xu et al., 2018) whereas DECP1 interacts with Rab18 to enhance LD production (Gao et al., 2019). NSP7 might recruit Rab18 and DFCP1 to enhance LD formation.

Enteroviruses were also reported to increase LD numbers. Indeed, upon infection, viral proteins 2B and 2C associate with LDs causing their clustering. Then, enteroviral protein 3A, localized on the membranes of ROs, facilitates the recruitment of ATGL. The increased lipase activity leads to the release of long-chain FAs and promotes synthesis of phospholipids that expands RO membranes (Belov and van Kuppeveld, 2019).

Thus, LDs can be envisioned as major sites of the cell-virus interplay and competition for resources, where lipids are stored and used to help fight infection, but whose membrane may be used directly as a platform where viral assembly is fuelled and favoured by the LD itself. For this reason, reducing the number of LDs with pharmacological inhibitors of DGAT or with PEA may be proposed to reduce replication and spread of different viral species (Alketbi et al., 2021; Da Silva et al., 2020; Fonnesu et al., 2022). This may allow off-label use of DGAT-2 inhibitors, like those in trial against hepatic steatosis [clinicaltrials.com] or DGAT-1 inhibitors that proved effective at reducing prostate cancer tumour growth (Nardi et al., 2019).

3.1. Viral infection and host lipidome

Whether LD numbers increase due to virally-induced direct or indirect mechanisms, they are used up by lipolysis and lipophagy during infection. Like infected cells, viruses need lipids to fuel their replication, therefore they upregulate lipid metabolism, to an extent that the host lipidomics may experience changes during viral infection, as noticed for HCV first, then also for other pathogens (Diamond et al., 2010; Feingold and Grunfeld, 2000; Hofmann et al., 2018; Leier et al., 2020; Oswal et al., 2022). Membrane remodelling leads to changes in the lipidomic profile of the whole liver during HCV infection, where steatosis may result after long term infection, especially genotype 3 (Sheridan et al., 2022). Interestingly, HCV 3a, and no other genotypes, capsid protein was shown to upregulate LD size by downregulating PTEN expression in hepatocytes (Fig. 1) (Clément et al., 2011). Because of its importance as a human pathogen, and the challenges posed by its study and control, HCV has been extensively studied (Luna et al., 2019). As it specifically infects hepatocytes, which are "professional" lipogenic cells, HCV has specialized in exploiting lipid metabolism. As other Flaviviridae, HCV modifies the membrane of the ER and LDs to create conspicuous DMVs and ROs through the action of specific viral proteins(Gu and Rice, 2013; Romero-Brey et al., 2012). As an example, HCV NS4B-induced ER stress, and the 3' end of viral genome, cause activation of SREBP-1 and the consequent transcription of lipid metabolism genes, such as FASN (Fig. 1) (Li et al., 2013; Park et al., 2009; Waris et al., 2007). It has long been known that HCV core protein localizes on the surface of LDs in a DGAT1-dependent manner (Camus et al., 2013), where viral RNA replication is temporally and spatially coupled to nucleocapsid formation (Lee et al., 2019), a phenomenon recently suggested also for SARS-CoV-2 (Scherer et al., 2022). Moreover, live imaging experiments showed that LDs are enveloped by ER membranes and associated with DMVs where HCV E2-NS5A structures were seen to be located at HCV assembly sites (Lee et al., 2019). In the late phases of infection, E1 and E2 envelope proteins may interact with these lipid-capsid complexes (Bartenschlager et al., 2011). On the whole, HCV influences the subcellular distribution of lipid kinases, increasing cholesterol and sphingolipid content in membranes (Bianco et al., 2012; Reiss et al., 2011). Infection leads to a reduction in the neutral: membrane lipid ratio, in other words, to an increase in cholesterol levels at the expenses of LDs (Diamond et al., 2010; Hofmann et al., 2018).

Lipidomic dysregulation has been noticed in serum from patients with severe COVID19 (Caterino et al., 2021; Shen et al., 2020). Lipid imbalance is thought to play a role in pathogenesis of COVID19; one reason is due to the influence of lipids in the differentiation of macrophages into the M1/M2 phenotype, given their role as main actors in inflammatory responses. In this regard, monocytes from COVID19 patients show a lipogenic phenotype due to increased expression of SREBP-1 and the nuclear receptor PPARγ, in turn upregulating CD36. Therefore, lipid uptake and LD numbers increase in SARS-CoV-2 monocytes (Da Silva et al., 2020). SREBP-1 is a key player of viral replication, when hijacked to this purpose, as recently shown on for a wide range of viruses (Yuan et al., 2019). Interestingly, PLA A2 group 2D- and prostaglandin D2 receptor knockout mice, lacking a PLA that is normally expressed in an age-dependent fashion and the prostaglandin D2 receptor respectively, cleared SARS-CoV-2 infection more rapidly than normal mice, showing the close connection between lipid metabolism, inflammation, age and SARS-CoV-2 replication/severity (Wong et al., 2022). In agreement with these results, Asapiprant, tested in phase 1–3 clinical trials against allergic rhinitis and asthma, is being tested as a novel anti-SARS-CoV-2 drug (https://clinicaltrials.gov/ct2/show/NCT04705597, s.d.).

4. Inflammation in the early stages of infection

4.1. Inflammatory lipids during viral infection

An evolutionarily conserved link exists between nutrient availability, lipid balance in cells, UPR and inflammation (Hotamisligil, 2017; Keestra-Gounder et al., 2016). The UPR brings about production of eicosanoid acids, like prostaglandins and leukotrienes and other lipidic mediators of inflammation (Calder, 2020). Eicosanoids are derivatives of arachidonic acid, a 20-carbon chain ω-6 polyunsaturated FA, obtained from diet or from the conversion of linoleic acid in the cytosol and incorporated as arachidonyl-phospholipids in cell membranes, starting from ER membranes then to all others (Hammock et al., 2020). Arachidonic acid is released from phospholipids by various PLAs, among which ATGL and cytosolic PLA-A2α (cPLA2α), a non-redundant member of the group IV A PLA family that has a major role in biosynthesis of eicosanoids(Adler et al., 2008). Once free, arachidonic acid can be converted to inflammatory mediators, like prostaglandins, prostacyclins and thromboxane by cyclooxygenases (COX1 and COX2) or to leukotrienes by lipoxygenases (Calder, 2020).

cPLA2α also generates another class of inflammatory lipids derived by membrane phospholipid and sphingolipid hydrolysis, called lysophospholipids (LPLs). LPLs are present in small amounts in biological membranes, where they are involved in remodelling and curvature, and membrane-protein interaction. This activity of LPLs is exploited by Coronaviridae, but not influenza or Picornaviridae: in CoV 299E-infected cells, where LPL accumulate to induce curving of the ER membrane during formation of ROs, DMV content was shown to be significantly downregulated after cPLA2α pharmacological inhibition, whereas higher LPL concentrations could be found in untreated infected cells (Müller et al., 2018). SARS-CoV-2 as well was proven to stimulate the synthesis of LPLs to support DMV biogenesis, with an involvement of its NSP4 and NSP6 (Alketbi et al., 2021). NSP4 is a membrane spanning protein participating in viral replication-transcription complex formation. Instead, NSP6 induces the formation ER-derived autophagosomes (Yadav et al., 2021). Proteomic analyses of infected cells have shown that MERS CoV also upregulates cPLA2α, to promote formation of DMVs and other membranous structures (Yan et al., 2019).

Given the fine link between synthesis of eicosanoids and lipid metabolism(Tilg et al., 2021), it is not surprising that viral infection turns on inflammation. Inflammation plays a major role in pathogenesis

of severe COVID19, with macrophages being implicated in most of the pathology (Merad and Martin, 2020; Wong et al., 2022). SARS-CoV-2-infected monocytes were shown to exhibit increased production of leukotrienes, chemokines, as well as inflammatory cytokines, including IL-6 and TNFα, in parallel with increased numbers of LDs. Inhibition of LD accumulation brought about a reduction in these inflammatory mediators, together with a reduction of viral replication (da Silva et al., 2020). Indeed, TG breakdown was recently shown to regulate macrophage inflammatory response (Morgan et al., 2021; van Dierendonck et al., 2022). Specifically, the accumulation of exogenous FAs as TGs and cholesterol esters is significantly higher in M1 macrophages, while enrichment in glycerophospholipids, ether lipids, and sphingolipids increases in M2 macrophages, indicating that SARS-CoV-2 may bend macrophage polarization by influencing the balance of these compounds (Morgan et al., 2021). In agreement, recent findings revealed that pharmacological inhibition of UPR in MERS-CoV-infected primary human lung endothelial cells ameliorated lung injury by slowing down apoptosis caused by UPR (Sims et al., 2021). To sum up, as a consequence of cPLA2α activation, Coronavirus infection brings about a higher content of several LPLs and FAs, together with eicosanoids (Fig. 2), proving that LDs are used for inflammatory mediator production in sync with viral replication.

Another class of inflammatory lipids is represented by sphingolipids, which will be discussed in the next Section.

4.2. The emerging role of lysosomes in inflammation and infection

While the role of lysosomes in lipid metabolism has long been explored in cancer research, their contribution is a relatively novel field in virology. Lysosomes contain many enzymes that are activated by acidic conditions to degrade DNA, proteins, carbohydrates, but also endogenous and exogenous lipids. This influences the balance of lipid at a cell level: the inhibition of lysosomal enzymes involved in lipid metabolism increased cellular LD content and cholesterol levels, for they proved to be essential for rapid TG turnover (Singh et al., 2009). Thus, lysosomes are emerging as important hubs for lipid sensing and signalling, and it is likely their lipid sensing and trafficking functions are intimately coupled. Specifically, lysosomes are one of the main sites of catabolism and balance of sphingolipids, such as sphingomyelin (SM) and its breakdown products, ceramides (CEs). These lipids are structural components of cellular membranes, with SM being the most abundant, but are also bioactive lipids regulating cell survival, proliferation, senescence and death (Hannun and Obeid, 2018). In lysosomes, CEs are produced by acid sphingomyelinase (SMase); then, they may be deacylated to sphingosine by acid CEase (Lai et al., 2021). In turn, sphingosine can move from lysosomes and be phosphorylated to sphingosine-1-phosphate (Sp1P) by sphingosine kinases (SKs) (Körner and Fröhlich, 2022). (Fig. 2). The balance between CEs and SM is kept by *de novo* synthesis of CEs, mostly in the ER, and by the scavenging pathway, mostly in lysosomes. Hence, lysosomes play a key role in lipolysis and lipophagy, and also promote lipid transport, critical in maintaining cellular lipid homeostasis (Fig. 2) (Thelen and Zoncu, 2017).

Several studies indicate that CEs, as well as CE-1-phosphate and Sp1P, are key activators of inflammation *via* activation of pro-inflammatory transcription factors in different cell types and production of pro-inflammatory prostaglandins by induction of COX-2 (Teichgräber et al., 2008). Because acid CEase only works at acidic pH, alkalinisation of lysosomes may lead to accumulation of CEs and inflammation (Fig. 2). It was recently shown that SARS-CoV-2 ORF3a promotes viral exocytosis by targeting lysosomes, suggesting that lysosomes are used to exit cells by SARS-CoV-2 (Chen et al., 2021; Ghosh et al., 2020; Yang et al., 2022). To achieve this, acidification is inhibited to inactivate lysosomal lytic enzymes, thus promoting inflammation by a strictly lysosomal dependent fashion.

The inflammatory response itself might lead to lysosomal CE accumulation. As an example, TNFα was shown to activate lysosomal acid SMase, resulting in CE production (Henkes et al., 2008). In macrophages, TNFα also activates the proinflammatory transcription factor NF-κB, in turn causing transcription of several proteins involved in inflammation, such as interleukin (IL)-1β, IL-6, IL-8 in addition to pro-inflammatory enzymes, such as COX-2 (Al-Rashed et al., 2021). As mentioned above, Sp1P, produced by SK (Fig. 2), activates inflammation in several cell types, where TNFα -induced upregulation of COX-2 expression and subsequent PGE2 production were dependent on activation of SKs (Pettus et al., 2003). SK1, but not SK2, was required for COX-2 induction. In addition, Sp1P and CE-1-P contribute to cPLA2 activation to produce prostaglandin (Pettus et al., 2005).

Sphingolipid metabolism is altered during infection by very different viruses, where CEs and SM play pivotal roles (Avota et al., 2021; Soudani et al., 2019). CEs and other sphingolipids affect the physicochemical properties of lipid membranes (Avota et al., 2021; Beckmann and Becker, 2021). For example, the incorporation of CEs can increase membrane rigidity by ordering the acyl chains, dividing the membrane into microdomains thus resulting in facilitated membrane fusion, fission, budding and vesicle formation. It is not surprising that ss + V, that extensively manipulate membranes, end up causing lipid unbalance and inflammation. Indeed, CEs are more abundant during ZIKV infection, where they seem to exert an essential function, probably in the ROs themselves (Leier et al., 2020) CEs also redistribute to WNV ROs where CE production *via* both *de novo* and salvage pathways is necessary for WNV replication (Aktepe et al., 2015). Also, SM and the CE Transfer protein are required for the biosynthesis of DMVs that HCV uses as replication sites (Gewaid et al., 2020). In contrast, CEs do not redistribute into DENV ROs, and the inhibition of CE synthase acts oppositely, enhancing DENV production (Aktepe et al., 2015). This evidence demonstrates that even viruses from the same genus may have different sphingolipid requirements for replication. Once these requirements are clarified, targeting sphingolipid-metabolizing enzymes offers interesting new opportunities for antiviral therapy. Inhibitors of CE biosynthesis, like fenretinide, have been reported to have anti-inflammatory *and* antiviral properties against a number of different viruses, including ZIKV, Rhinoviruses, Coronaviruses, and non-ss + V like Retroviruses (Finnegan and Blumenthal, 2006; Pitts et al., 2017). Interestingly, lack of lysosomal enzyme acid ceramidase (CEase) in macrophages has been demonstrated to be beneficial to Herpes simplex virus replication (Lang et al., 2020a,b). It may be speculated that also the inhibitor of acid CEase Carmofur, a well-established adjuvant drug in cancer treatment, might exert opposite activity on selected viral species (Fig. 2) (Lai et al., 2019).

Sphingolipids have a major role in regulating virally induced apoptosis. While halting viral replication, apoptosis may contribute to viral spread by causing tissue injury and blunting the immune response (Danthi, 2016). Encephalomyelitis due to Sindbis virus-induced neuronal killing and HIV-1-induced neuronal apoptosis are examples of how virally induced cell death might contribute to morbidity. In both cases, apoptosis activation is dependent on lysosomal sphingomyelinase activation and generation of long-chain CEs by both *de novo* and scavenging pathways (Beckmann and Becker, 2021).

Because of the multifarious role of lysosomes in the metabolism of lipids, they can be targeted for the design of drugs that may also affect inflammation at the same time as viral replication. For instance, we and others have obtained results showing that N-acylethanolamines (NAEs), a class of lipidic inflammatory mediators derived from FAs and ethanolamine, may affect replication of several viral species (Carpinteiro et al., 2020; Lai et al., 2021; Lang et al., 2020a,b; Tsuboi et al., 2018). Among NAEs, PEA is an endogenous amide widely present in all mammalian cells. The major pathway for PEA degradation is its hydrolysis to free FAs and ethanolamine by the lysosomal enzyme NAE-hydrolyzing acid amidase (NAAA), as shown in macrophages and peripheral tissues (Ribeiro et al., 2015; Sasso et al., 2018). As mentioned in Section 3, PEA exerts its anti-inflammatory effects mainly by acting as an agonist of PPAR-α, thereby promoting the induction of β-oxidation of

FAs produced during lipophagy (Fig. 2). PEA, therefore, actively counteracts replication of those viruses relying on the formation of LDs, like SARS CoV2 (Fonnesu et al., 2022; Zimniak et al., 2021) Other drugs sequestered in lysosomes may have antiviral effects: Zimniak et al. (2021) studied the anti-SARS-CoV-2 effect of fluoxetine, normally used as a serotonin reuptake inhibitor to treat depression, that is trapped in lysosomes (Lu et al., 2017). They found that it deeply and specifically suppresses SARS-CoV-2 replication in human lung tissue, independently from serotonin reuptake. Whatever the mechanism is, they confirm that lysosomes may be important targets for antiviral therapy.

Independently from their role in inflammation, lysosomes have been shown to play a role in the massive rearrangement of the host lipid balance essential for RO formation. As an example, HCV ROs are formed by the intervention of lysosomal proteins, such as the Nieman-Pick type protein C1, which requires cholesterol to transfer lipids to ROs. Pharmacological inhibition of Nieman-Pick type protein C1 reduces virus replication (Stoeck et al., 2018). In agreement with this observation, modifications of membrane lipid proportions contribute to the formation of HCV membranous web, that turns out to be enriched in cholesterol (Mingorance et al., 2018).

The advantage of lysosomal antiviral drug targeting would be that drugs may be delivered to lysosomes by receptor-mediated endocytosis, in addition to lysosome-targeting receptors and other strategies, enhancing selectivity and diminishing drug degradation inside cells (Sharma et al., 2018).

5. Conclusions

Lipid metabolism may be envisioned as a new frontier for the design of antiviral drug development. The advantage of this strategy resides in the presence of many drugs already approved to act on lipid metabolism for a plethora of human diseases that span from cancer to diabetes and inflammation. Indeed, many of them may be repurposed as antivirals. Many recent reports underlines that the role of lipids in viral replication is pivotal: because different viruses may hijack the same cellular factors involved in lipid metabolism, identifying these factors may pave the way to the design of broadly-acting antiviral molecules. On the other hand, specific antiviral drugs may be designed to target the viral genes that physically hijack cellular mediators involved in lipid metabolism. To this aim, dissecting the role of the various lipids in viral replication and inflammation is vital, above all because these may change from one virus to another and in different cell types.

Since release of lipid inflammation mediators derived from eicosanoids is strictly linked to lipid metabolism, targeting the balance of different lipids to inhibit viral replication may also have the advantage of quenching inflammation and vice versa. This might be beneficial in diseases like COVID19, where deranged inflammatory responses are hallmarks of severity. In light of these considerations, unravelling the relative importance of cellular factors in inflammation and viral replication is considered a priority in the field. In this context, lysosomes are being indicated as pivotal elements in cellular lipid balance and inflammation. Because many drugs end up in lysosomes, and lysosomes can be specifically targeted due to their unique properties, they may be envisioned as additional targets of antiviral therapy.

Finally, to end the inflammatory response, it is important that resolution runs in an ordered fashion. A central mechanism involved is the generation of pro-resolving lipid mediators which act to inhibit inflammatory signalling (Chiurchiù et al., 2022). Switch in lipid type production may be aided by specific drugs, thus contributing to quenching virally-induced inflammation when this becomes excessive.

Author contributions

ADC, MS, EI, CF, VLR, GL, CP, PQ review of the literature; writing. ML, GF visualization. ML, MP, GF writing—review and editing. GF supervision. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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