Chapter 19

Peroxisomes and Viruses: Overview on Current Knowledge and Experimental Approaches

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Abstract

The general interest in the study of the interplay between peroxisomes and viruses has increased in recent years, with different reports demonstrating that distinct viruses modulate peroxisome-related mechanisms to either counteract the cellular antiviral response or support viral propagation. Nevertheless, mechanistical details are still scarce, and information is often incomplete. In this chapter, we present an overview of the current knowledge concerning the interplay between peroxisomes and different viruses. We furthermore present, compare, and discuss the most relevant experimental approaches and tools used in the different studies. Finally, we stress the importance of further, more detailed, and spatial-temporal analyses that encompass all the different phases of the viruses' infection cycles. These studies may lead to the discovery of novel peroxisome-related cellular mechanisms that can further be explored as targets for the development of novel antiviral therapies.

Key words Peroxisomes, Virus, Peroxisome metabolism, Peroxisome biogenesis, Viral infection, Innate immunity, MAVS, Antiviral response

1 Introduction

Viruses are totally dependent on the host cell machinery for replication and dissemination. Throughout infection, different intracellular organelles are modulated by both the virus and the cellular immune system, becoming central players on the intricate virus-host interplay. As crucial organelles for the regulation of lipid and reactive oxygen/nitrogen species metabolism [1–3], peroxisomes have been shown to play important roles in the context of infection by different viruses.

Peroxisomes harbor the mitochondrial antiviral signaling adaptor protein (MAVS) and, in concert with mitochondria, are important platforms for the establishment of the cellular antiviral immune response [4]. Upon infection, viral RNA is detected by the cytosolic retinoic inducible gene-I (RIG-I)-like receptors (RLR), which undergo conformational changes and interact with MAVS,

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inducing its oligomerization. This prompts a signaling cascade that culminates with the production of interferons (IFNs) and IFN-stimulated genes (ISGs), inhibiting important steps of the virus life cycle [4–6]. Peroxisomal and mitochondrial MAVS perform complementing functions within the antiviral response: while the peroxisomal MAVS induces the rapid expression of defense factors providing short-term protection, the mitochondrial MAVS activates a signaling pathway with delayed kinetics that amplifies and stabilizes the antiviral response [4].

Different viruses have been shown to modulate peroxisome biogenesis and metabolism to not only evade the cellular antiviral response but also promote virus particle formation and propagation [7]. However, research in this field is still incomplete, and mechanistical details are scarce.

In this chapter, we present an overview of the state of the art concerning the interplay between peroxisomes and viruses as well as of the different experimental approaches and tools that were used to perform these studies. We present detailed data for different viruses and virus families and discuss how specific methodologies and experimental setups could be applied to fill in the gaps in knowledge concerning the role of peroxisomes in the context of specific viral infections, as well as how the obtained results could be extrapolated to other members of the same family.

2 Interplay Between Peroxisomes and Viruses

In the following sections, we present the current knowledge on the interplay between peroxisomes and different viruses. At the end of each section, we introduce a summarizing table, which also includes details on the experimental setups used in each study, such as tools, methodologies, and, importantly, the timepoints upon infection in which the analyses were performed. Figure 1 presents an overview on how the different viruses have been shown to interfere with peroxisomes throughout the different phases of their infection cycle.

2.1 Influenza A Virus (IAV)

The *Influenza A virus* (IAV), a member of the *Orthomyxoviridae* family, is a negative-sense single-stranded RNA (ssRNA) virus that can cause acute respiratory problems [8]. Upon infection, receptor-mediated endocytosis allows the release of the viral ribonucleoprotein complexes into the cytoplasm, which are then transported to the nucleus where genome replication and transcription take place. Translation of the other viral proteins by the host cell machinery leads to the assembly of new virus particles and formation of the viral envelope at the plasma membrane, synchronously to the export of the new virions from the cell [9, 10].

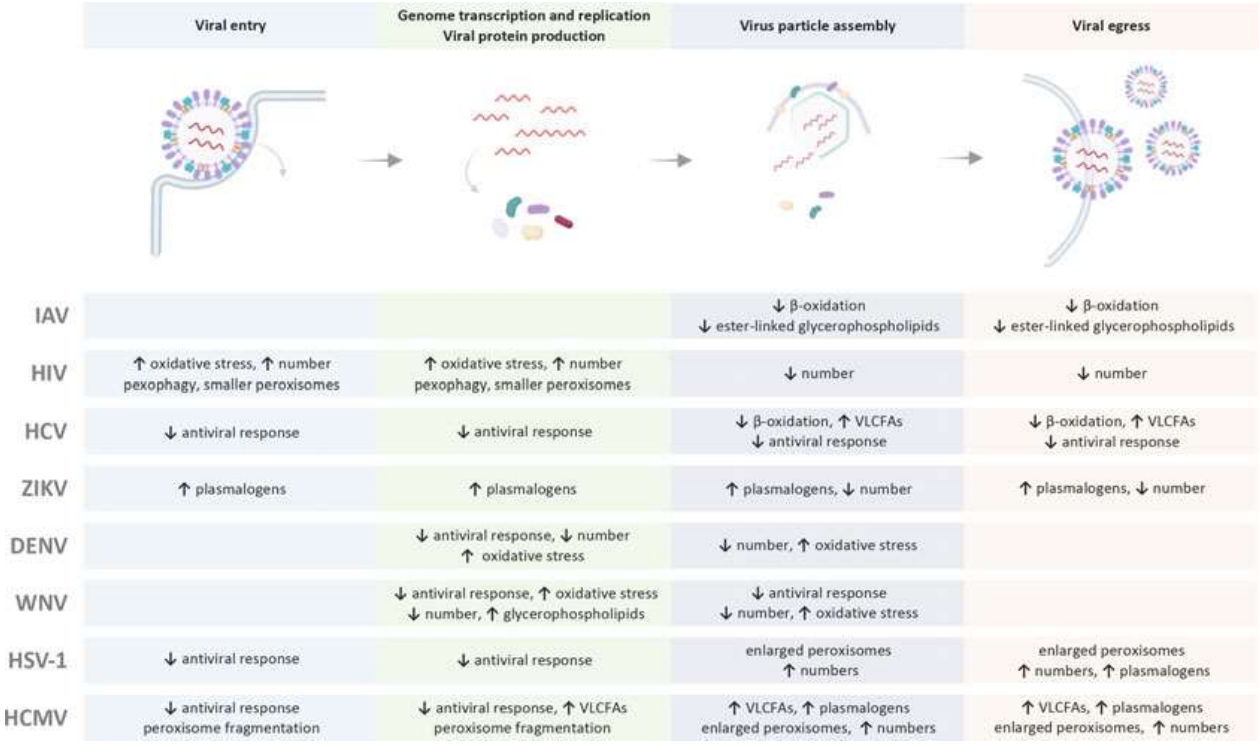

Fig. 1 Interplay between peroxisomes and viruses throughout the different phases of the infection cycle

Table 1
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the influenza A virus (IAV)

Cells and animal models	Peroxisome metabolism alterations		Infection timepoints	Methods used	Refs.
	β-oxidation	Lipids			
A549, CHO-K1 and NRel-4 cells, mice	Decreased	Lower levels of ester-linked glycerophospholipids; increase in ether-linked phosphatidylcholines	12, 18, 24 h	HPLC-MS/MS, plaque assay, catalase assay	[11]

Like other viruses, IAV depends on the host cell lipid metabolism for the efficient production of new virus particles. Interestingly, specific peroxisomal lipid metabolism modifications have been associated with IAV infection (Table 1 and Fig. 1). Using different omics studies, Tanner and colleagues [11] reported an enrichment of peroxisome-derived ether-linked lipids in the virus lipidic envelope. An impairment of β-oxidation was also observed during IAV infection. Interestingly, the IAV protein NS1 has been reported to interact with HSD17B4 (also known as DBP), a cellular protein that plays an important role in peroxisomal β-oxidation [12]. Although research on the interplay between IAV and peroxisomes is still scarce, the data seems to indicate that this virus may take advantage of peroxisome metabolism to promote an efficient

formation of new infectious particles. It is, however, important to notice that these studies were performed either at late stages of the infection cycle, when virus particles are already formed, or even using cells displaying different cycles of infection. It is hence necessary to expand these studies to the analysis of specific and earlier time points of a single infection cycle, to infer in more detail on the relevance of peroxisomes for IAV infection.

2.2 Members of the Coronaviridae *Family*

The members from the *Coronaviridae* family contain large positive-sense ssRNA genomes and include several important and medically relevant viruses such as the severe acute respiratory syndrome coronavirus (SARS-CoV), the SARS-CoV-2, and the Middle East respiratory syndrome coronavirus (MERS-CoV). The first step of *Coronaviridae* infection relies on the recognition of the spike protein by host cell receptors, followed by the release of the viral RNA into the cytoplasm. These viruses remodel the host cellular membranes to form viral replication organelles, usually double-membrane vesicles derived from the endoplasmic reticulum (ER), where RNA synthesis takes place. The newly formed virus particles bud into the ER-Golgi intermediate compartment and exit the cell via the secretory pathway [13, 14]. Little research has been conducted on the function of peroxisomes throughout *Coronaviridae* infections (Tables 2 and 3). Nevertheless, some interesting data has been shown for SARS-CoV-2 and two porcine coronaviruses.

2.2.1 *Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2)*

Upon 24 h of SARS-CoV-2 infection, peroxisomes were shown to be more abundant and redistributed to the viral replication sites at the perinuclear region [13]. The authors proposed that this redistribution could represent a strategy to either evade oxidative damage of the viral RNA during replication, manipulate antiviral

Table 2
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the severe acute respiratory syndrome coronavirus (SARS-CoV-2)

Cells	Peroxisomal alteration upon infection		Other obs.	Infection timepoints	Methods used	Refs.
	Biogenesis	Localization				
Calu-3, A549-ACE2	Increased number	Redistribution to perinuclear sites		16, 24 h	FIB-TEM, Western blot, confocal microscopy	[13]
Huh7, SK-N-SH	Reduced number	Redistribution to perinuclear sites	ORF9c-PEX14 interaction; loss of metabolic function	24, 48, 72 h	RT-qPCR, Western blot, confocal microscopy	[15]

Table 3
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the porcine deltacoronavirus (PDCoV) and porcine epidemic diarrhea virus (PEDV)

Virus	Cells	Peroxisomal alteration upon infection		Infection timepoints	Methods used	Refs.
		Antiviral signaling	Biogenesis			
PEDV	IPEC-DQ, LLC-PK1, MARC-145	Inhibition of IRF1-mediated type III IFNs response	Reduced number	3, 6, 9, 12, 18, 24, 36, 48 h	$TCID_{50}$, Western blot, confocal microscopy, RT-qPCR	[16]
PDCoV	LLC-PK1, IPI-2I	Inhibition of IRF1-mediated type III IFNs response	Reduced number	6, 12, 24 h	Confocal microscopy, RT-qPCR, Western blot	[17]

signaling, or control lipid metabolism. However, the underlying mechanisms are still unknown. Contrarily to these data, Knoblach et al. [15] observed a 50% decline in peroxisome abundance after 24 h of infection, with a continuous decline to up to 80–90% after 72 h. The authors have shown that the viral protein ORF9c interacts with the peroxisomal biogenesis protein PEX14, potentially hindering the import of peroxisomal matrix proteins and thus reducing peroxisome numbers and inducing loss of function [15]. The differences between the studies described above may not only reflect the use of distinct cell lines but also distinct timepoints of infection (Table 2). In fact, a focused ion beam scanning electron microscopy approach revealed that SARS-CoV-2 can complete its life cycle in a single cell in under 12 h [13]. Therefore, to conclude on the relevance of peroxisomes for SARS-CoV-2 infection and on the mechanistical details involved, more detailed studies should be performed throughout the different phases of a single infection cycle.

2.2.2 Porcine Deltacoronavirus (PDCoV) and Porcine Epidemic Diarrhea Virus (PEDV)

The porcine deltacoronavirus (PDCoV) and the porcine epidemic diarrhea virus (PEDV) are swine enteric coronaviruses. Studies involving both PEDV and PDCoV showed a decrease in peroxisome numbers to 30–50% and 20%, respectively, and an impaired antiviral response upon infection [16, 17] (Table 3). This reduction in peroxisome numbers during infection was proposed to compromise the IRF1-mediated type III IFN response downstream of MAVS, a process that the authors suggest to be mediated, in the case of PEDV, by the viral protein NSP1 [16].

2.3 Rotavirus

The rotavirus belongs to the *Reoviridae* family and is a double-stranded RNA (dsRNA) virus, responsible for viral gastroenteritis [18–20]. Upon entry and genome release into the cytoplasm, mature positive-sense ssRNA transcripts are synthetized, which undergo either replication into dsRNA or translation into viral proteins. Afterwards, viral inclusion bodies (named viroplasms) are formed, where further replication and assembly take place. Upon the formation of double-layered particles, these exit the viroplasms and are enveloped by the ER. At the final stage, the virus particle is released by cell lysis (reviewed in [21]).

Rotavirus was the first human virus to be linked to peroxisomes. Mohan and colleagues [22] demonstrated that the viral protein VP4 includes the canonical PTS1 signal at its C-terminus. Moreover, it was observed by laser scanning confocal microscopy that VP4 colocalizes with peroxisomes after 24 h of infection, in a PTS1-dependent manner. It was then proposed that this virus may cooperate with peroxisomes to favor viral infectivity, by interfering with either the lipid metabolism or posttranslational protein modifications [22]. Supplementary studies are needed to further clarify the role of peroxisomes in rotavirus infections.

2.4 Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus (HIV) is a positive-sense ssRNA virus that belongs to the *Retroviridae* family. It induces continuous failure of the immune system, leading to an acquired immunodeficiency syndrome, known as AIDS [23, 24]. During infection, HIV enters the cells and reversely transcribes the RNA to dsDNA in the cytoplasm. The DNA is transported to the nucleus and incorporated into the cellular genome [25]. At this point, the virus may remain in a latent stage, evading antiviral signaling by the host cells, or undergo transcription, translation, and viral packaging, before exiting the cell [26].

Although research on the involvement of peroxisomes in HIV infections is limited, the reported findings (Table 4 and Fig. 1) suggest that the virus modulates peroxisomes to evade antiviral signaling. HIV has been shown to impair peroxisomal biogenesis, reducing the total number of peroxisomes per cell [28–30]. Furthermore, HIV upregulates microRNAs that target the peroxisome biogenesis factors PEX2, PEX7, PEX11β, and PEX13 [29], decreasing their expression in primary macrophages, lymphocytes, and brain tissues [28, 29]. The viral protein Vpu has been shown to be crucial and sufficient for this microRNAs upregulation, demonstrated upon both Vpu ectopic expression and viral infection in different cell types. The authors suggest that this downregulation of peroxisome biogenesis may not only interfere with the early peroxisome-dependent antiviral signaling [28] but also, given the association between defects in peroxisome biogenesis and neuropathologies [1, 31], be associated with HIV-related neuropathological diseases [7, 28, 29]. In addition, in Vpu-expressing cells, the

Table 4
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the human immunodeficiency virus (HIV)

Cells	Peroxisomal alteration upon infection			Other obs.	Infection timepoints	Methods used	Refs.
	Metabolism	Biogenesis	Morphology				
3 T3				Nef co-localizes with ACOT8 at peroxisomes	48 h	Radiochemical assay, Northern-blot, confocal microscopy	[27]
Brain tissue from patients, primary macrophages (HeLa $CD4^+$), primary monocyte-derived macrophages	Catalase unaffected	Reduced number; less peroxisomal proteins	Altered		48 h, 72 h, 5 d	Western blot, confocal microscopy, immunochemistry, miRNA microarray	[28]
HeLa-CD4/CXCR4/CCR5 cells, primary monocyte-derived macrophages	Catalase unaffected	Reduced number; less peroxisomal proteins			48, 72 h	Confocal microscopy, Western blot, RT-qPCR, modified copper-triethanolamine assay	[29]
LC3B, HEK293, HEK/CD4.403/CXCR4	Oxidative stress: less catalase	Increased number	Smaller	Pexophagy	24, 48 h	Western blot, flow cytometry, RT-qPCR, Oxyblot and DHR123 assays, confocal microscopy	[30]

levels of non-esterified fatty acids were increased by twofold, compared to non-transfected cells [29]. Hence, peroxisomal metabolism may also be somewhat modulated during HIV infection.

Oxidative stress increases the risk for HIV-1-associated disorders. Evidence shows that HIV patients have depleted levels of antioxidant enzymes, such as glutathione and superoxide dismutase, and elevated ROS levels (reviewed in [32]). Additionally, transfection of lymphocytes with Env, the HIV envelope protein, induced an impairment in the expression of catalase and PEX14 after 24 h [30]. Env has also been shown to induce a decrease in peroxisome numbers by pexophagy and the accumulation of ROS in uninfected bystander $CD4^+$ T lymphocytes, leading to their death by apoptosis [30]. Furthermore, the viral protein Nef localizes at peroxisomes and interacts with ACOT8 [27, 33], a thioesterase involved in the regulation of acyl-CoA/CoASH at peroxisomes [34]. However, others have reported that catalase expression was unaltered upon 48 h of HIV infection [28, 29].

Additional studies are required to better understand the interplay between HIV and peroxisomes, either regarding the antiviral response, cellular oxidative stress, or the influence of peroxisome metabolism in the formation of new virus particles or disease progression. This research should also be extended to other members of the *Retroviridae* family, for which nothing has been reported regarding this interplay.

2.5 Enterovirus 71

The enterovirus 71 (EV71) is a positive-sense ssRNA non-enveloped virus that belongs to the family of *Picornaviridae*. It causes hand, foot, and mouth disease, frequently evolving to neuronal pathogenesis [35–37]. Upon infection, the viral genome is released into the cytoplasm where it undergoes replication and translation. This virus induces a rearrangement of the ER to form compartmentalized replication organelles, where replication takes place (reviewed in [38]).

Yeast two-hybrid screening coupled with co-immunoprecipitation (co-IP) analyses revealed that the viral protein 3D interacts with ACOX1 [39] (Table 5). 3D seems to be responsible for a downregulation and declined expression of ACOX1 and PEX14 in neuroblastoma and human astrocytoma cells. Furthermore, the authors describe that ACOX1 expression impairs EV71 replication, while its knockdown diminishes viral cytopathic effects on the host cells [39]. While further research should be performed to confirm these assumptions, the authors suggest that the downregulation of ACOX1 and PEX19, which leads to a reduction in peroxisome number and, consequently, the accumulation of ROS, triggers the induction of autophagy and apoptosis, to ultimately favor the release of new virus particles [39].

Table 5
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the enterovirus 71 (EV71)

Cells	Peroxisomal alteration upon infection			Other obs.	Infection timepoints	Methods used	Refs.
	Metabolism	Biogenesis	Proteins				
RD, U251, HEK293T, SK-N-SH	ROS accumulation	Reduced number	Downregulation of ACOX1 and PEX19	ACOX1 expression impairs EV71 replication	12, 18, 24, 48, 72 h	RT-qPCR, Western blot, co-IP, confocal microscopy, flow cytometry, yeast-two hybrid	[39]

2.6 Members of the Herpesviridae *Family*

Herpesviridae is a family of dsRNA enveloped viruses that can cause severe diseases in humans [40–43]. This family is divided into three subfamilies: *α-herpesvirinae*, *β-herpesvirinae*, and *γ-herpesvirinae*. The *α-herpesvirinae* viruses have a short life cycle and this subfamily includes the most prevailing herpesvirus—herpes simplex virus (HSV-1). Contrarily, infection by viruses from the *β-herpesvirinae* subfamily, such as the human cytomegalovirus (HCMV), progresses slowly, and the infected cells survive, increasing in size. The *γ-herpesvirinae* subfamily includes the Kaposi's sarcoma-associated herpesvirus (KSHV).

Upon entering the host cell, the viral DNA enters the nucleus, where DNA transcription, replication, and assembly occur. *Herpesviridae* viruses can then achieve a latent phase in which the DNA remains circular, inhibiting viral replication, and silent until the lytic phase is reactivated [44]. The duration of the infection cycles varies greatly between different viruses of this family, with, e.g., HSV-1 and HCMV taking about 20 and 120 h to form new virus particles, respectively [44].

2.6.1 Human Cytomegalovirus (HCMV)

HCMV is the virus that has received more attention concerning the importance of peroxisomes for the proper development of the infection cycle, with robust and complete spatial-temporal data arising from different studies (Table 6 and Fig. 1).

HCMV infection has been shown to induce a continuous accumulation of peroxisomal proteins, specifically proteins involved in peroxisome biogenesis (PEX3, PEX6, PEX13, PEX14), from early to late phases of infection [47, 50]. Peroxisome numbers have also been revealed to increase by 3.6-fold in infected cells at 96 h post-infection [50]. Interestingly, the induction of peroxisome biogenesis with 4-phenylbutyrate (4-PBA) resulted in an enhancement of viral replication and assembly by sevenfold [50]. Furthermore, PEX3, PEX7, and PEX19 knockouts lead to dampened HCMV replication [46, 50]. The authors have also shown differences in peroxisome size throughout infection: fragmentation at early time points and increase in size at late infection stages [49, 50]. The viral protein vMIA (also known as pUL37x1) has been shown to play an important role in these morphological changes, through activation of PEX11β [49]. vMIA has also been shown to interact with PEX19 in order to be transported to the peroxisomal membranes, where it interacts with MAVS and inhibits its oligomerization, compromising downstream antiviral signaling [48, 51].

Peroxisome lipid metabolism has also been shown to be altered during HCMV infection. Fatty-acid-activating enzymes and elongases are upregulated after 48 h, and several long-chain acyl-CoA synthetases were revealed to be required for HCMV replication [45]. HCMV infection was also shown to increase the synthesis of

Table 6
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the human cytomegalovirus (HCMV)

Cells	Peroxisomal alteration upon infection			Other obs.	Infection timepoints	Methods used	Refs.
	Antiviral signaling	Biogenesis	Metabolism				
MRC5			Increase in VLCFAs	HCMV virions depend on VLCFAs metabolism	48, 72, 96 h	PCR-arrays, Western blot, plaque assay, LC-MS, RT-qPCR	[45]
CRL-1634				Increase in PEX3 levels; PEX3 required for viral replication	5, 12, 24, 72 h	RNA-seq, ribosome profiling, Western blot, $TCID_{50}$	[46]
Primary human fibroblasts				Accumulation of peroxisomal proteins	24, 48, 72, 96, 120 h	MS in peroxisomal fraction, confocal microscopy	[47]
HepG2, HFF, MEFs	vMIA interacts with peroxisomal MAVS, inhibiting downstream signaling	vMIA induces peroxisome fragmentation		vMIA interacts with PEX19 and localizes at peroxisomes	8, 24 h	Western blot, confocal microscopy, co-IP, RT-qPCR	[48]
HFF-1		Early infection: vMIA induces peroxisomal fragmentation; late infection: enlarged peroxisomes		vMIA localized in fragmented peroxisomes	24, 48, 72, 96, 120 h	LC-MS/MS, confocal microscopy, Western blot, IP	[49]

(continued)

Table 6
(continued)

Cells	Peroxisomal alteration upon infection			Other obs.	Infection timepoints	Methods used	Refs.
	Antiviral signaling	Biogenesis	Metabolism				
MRC5, peroxisome biogenesis disorder dermal fibroblasts		Increased number; Early infection: peroxisomal fragmentation; late infection: enlarged peroxisomes	Upregulation of ether lipid and plasmalogen synthesis at late infection phases	Peroxisomal proteins accumulation; Viral replication depends on peroxisome abundance	6, 24, 48, 72, 120 h	MS, confocal and live microscopy, Western blot	[50]

Table 7
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the herpes simplex virus 1 (HSV-1)

Cells	Peroxisomal alteration upon infection		Other obs.	Infection timepoints	Methods used	Refs.
	Antiviral signaling	Biogenesis				
HEK293, HEK293T, MEFs	Early stage: inhibition of antiviral response			18 h	RT-qPCR, Western blot	[52]
MRC5, peroxisome biogenesis disorder dermal fibroblasts		Increased number of enlarged peroxisomes late in infection	Viral replication depends on peroxisome abundance	16 h	Mass spectrometry, confocal microscopy, Western blot	[50]

very-long-chain fatty acids (VLCFAs) and the production of plasmalogens, which are required for infectious virus particles' formation [45, 50].

These studies clearly illustrate a dynamic interplay between peroxisomes and HCMV throughout the different stages of the infection cycle: the virus interferes differently with peroxisome morphology and metabolism to inhibit the peroxisome-dependent antiviral signaling early in infection and to promote replication and particle formation at later infection stages.

2.6.2 Herpes Simplex Virus 1 (HSV-1)

As described above, the HSV-1 life cycle is shorter than the one of HCMV, lasting 18–20 h [44]. Like HCMV, HSV-1 has also been found to evade the downstream signaling from peroxisomal MAVS (Table 7 and Fig. 1). Although the mechanisms involved are not yet disclosed, the authors demonstrate that, at early infection stages, the viral protein VP16 impairs the immediate early antiviral signaling, contributing to HSV-1 proliferation [52]. Importantly, an increase in peroxisome numbers and morphologic alterations was observed mainly at late infection stages [50]. Although further studies are needed to unravel the interplay between HSV-1 and peroxisomes, these results seem to pinpoint to a comparable modulation of peroxisomal mechanisms by both HCMV and HSV-1.

2.6.3 Kaposi's Sarcoma-Associated Herpesvirus (KSHV)

The interplay between peroxisomes and KSHV was only studied in the context of latent infection (Table 8). Nevertheless, important results were obtained showing an increase of about 50% in peroxisome numbers as well as the upregulation of ABCD3, also known

Table 8
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the Kaposi's sarcoma-associated herpesvirus (KSHV)

Cells	Peroxisomal alteration upon infection		Other obs.	Infection timepoints	Methods used	Refs.
	Antiviral signaling	Biogenesis				
BCBL-1, HEK293T	Peroxisomal MAVS stabilizes the expression of vFLIP	–	vFLIP is targeted to peroxisomes; MAVS-vFLIP interaction is essential for the survival of latently infected cells	24, 96 h	Western blot, co-IP, confocal microscopy, RT-qPCR	[53]
TIME, hDMVECs, LECs	–	Increased number	Upregulation of ABCD3 and increase of PEX3	48, 96 h	Confocal microscopy, MS/MS, RNA-seq, flow cytometry	[54]

as PMP70, and increased levels of PEX3 [54]. The authors demonstrated that latency genes are sufficient for the induction of ABCD3 expression. In addition, docosahexaenoic acid (DHA) and its precursors, mainly produced during peroxisomal β-oxidation, appear upregulated during KSHV latency. Loss of ACOX1, an important enzyme for DHA metabolism, and ABCD3, crucial for VLCFAs transport, enhanced mortality of KSHV-infected cells at 96 h post-infection. DHA production by peroxisomes may hence be required for KSHV pathogenesis.

KSHV has also been shown to interfere with peroxisomes at the level of the antiviral response. Peroxisomal MAVS interacts with the viral protein vFLIP, which localizes at peroxisomes in a PEX19-dependent manner and stabilizes its expression. This interaction is essential to maintain infection and establish latency in infected cells [53].

KSHV seems to, hence, modulate peroxisome metabolism and morphology to its own benefit. Further studies in infected non-latent cells should be performed to further unravel the importance of this interplay for the production of newly infectious virus particles and dissemination of infection.

2.7 Members from the Flaviviridae *Family*

The members from the *Flaviviridae* family are small enveloped positive-sense ssRNA viruses that are totally dependent on the host lipid metabolism for the formation of new virus particles [55, 56]. Upon infection and receptor-mediated endocytosis of

the viral particle, the viral genome is released into the cytoplasm where it undergoes replication and translation. These viruses induce remarkable ER rearrangements to form compartmentalized replication organelles, which facilitate the concentration of enzymes and substrates for higher reaction efficiency and the regulation of virus assembly and protect the viral genome from recognition by the host cell immune system [57, 58].

The genus *Flavivirus* includes mosquito-borne viruses such as dengue virus (DENV), West Nile virus (WNV), and Zika virus (ZIKV), which pose a global health concern. Another important member from this family, belonging to the *Hepacivirus* genus, is the hepatitis C virus (HCV), which can cause both acute and chronic hepatitis C, eventually leading to liver cirrhosis, fibrosis, or even hepatocarcinoma [55].

Although not much is known concerning the interplay between peroxisomes and *Flaviviridae*, some reports have shown a direct interference with the peroxisome-dependent antiviral signaling as well as peroxisome metabolic and morphological alterations during infection.

2.7.1 Dengue Virus (DENV)

DENV has been shown to impair peroxisome biogenesis, decreasing the abundance of these organelle during early infection stages (Table 9 and Fig. 1) [59, 60]. The authors suggest that the reduction in peroxisome abundance by flaviviruses may influence the antiviral response by inducing suppression of type III IFNs [59].

The DENV capsid protein interacts with PEX19, resulting in a reduction of the amount of this and other peroxisomal proteins in infected cells [59]. A redistribution of PEX19 to capsid-positive juxtanuclear positions was also observed [59]. However, despite this interaction, no peroxisomal targeting of the capsid protein has been observed [60]. DENV infection has also been shown to induce a reduction in catalase expression (>15%) from 16 to 48 h post-infection [59].

2.7.2 West Nile Virus (WNV)

Infection by WNV has revealed very similar results to the ones obtained upon infection with DENV (Table 10 and Fig. 1), leading to a decrease in peroxisome number and disruption of the type III IFN response [59]. WNV capsid protein has also been shown to interact with PEX19 [59]. WNV infection further results in the accumulation of intracellular glycerophospholipids [61] and a reduction in catalase expression from 16 to 48 h post-infection [61].

2.7.3 Zika Virus (ZIKV)

Although comparable to other flaviviruses, ZIKV infections have been more thoroughly studied (Table 11 and Fig. 1). At 24 h post infection, ZIKV caused a 60–70% decrease in peroxisome numbers, and a 30% reduction was also observed upon overexpression of the viral capsid protein [62]. In agreement, Coyaud and colleagues

Table 9
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the dengue virus (DENV)

Cells	Peroxisomal alteration upon infection				Other obs.	Infection timepoints	Methods used	Refs.
	Metabolism	Antiviral signaling	Biogenesis	Protein localization				
A549, HEK293T	Decreased catalase expression	Impairment of type III IFNs response	Reduced number	PEX19 is redistributed to capsid-positive juxtanuclear positions	PEX19 knockdown reduces viral titer and replication; Capsid-PEX19 interaction leads to PEX19 degradation	16, 24, 48 h	LC-MS, confocal microscopy, co-IP	[59]
HFFF, A549, PEX19- and PEX3-deficient human skin fibroblasts			Reduced number		Lack of PEX3 and PEX19 compromises DENV replication	24, 48, 72 h	Plaque assay, GST-pull down assay, confocal microscopy	[60]

Table 10
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the West Nile virus (WNV)

	Peroxisomal alteration upon infection							
Cells	**Metabolism**	**Antiviral signaling**	**Biogenesis**	**Protein localization**	**Other obs.**	**Infection timepoints**	**Methods used**	**Refs.**
A549, HEK293T	Decreased catalase expression	Impairment of type III IFNs response	Reduced number	PEX19 is redistributed to capsid-positive juxtanuclear positions	PEX19 knockdown reduces viral titers and replication; Capsid-PEX19 interaction leads to its degradation	16, 24, 48 h	LC-MS, confocal microscopy, co-IP	[59]
HeLa	Increase in glycerophospholipids					24 h	TEM, confocal microscopy, UPLC, LC-MS	[61]

Table 11
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the Zika virus (ZIKV)

Cells and patients	Peroxisomal alteration upon infection			Other obs.	Infection timepoints	Methods used	Refs.
	Metabolism	Biogenesis	Protein localization				
Primary human fetal astrocytes, A549, HEK293T, Vero, U251		Reduced number		Viral titers and replication reduced upon overexpression of PEX11β; capsid-PEX19 interaction; capsid overexpression decreases PEX19 levels; reduction of peroxisomal proteins levels	24, 48 h	LC-MS, co-IP, Western blot, confocal microscopy	[62]
Vero, HeLa		Reduction of peroxisome density	NS2A interacts with PEX3 and PEX19, thus it is localized at peroxisomes	Decrease of PMP70 levels; peroxisomes are required for viral replication	3 d	BioID, IP-MS	[63]
Patients	Increased plasmalogen levels				–	LC-MS	[64]
HFF, A549, PEX19- and PEX3-deficient human skin fibroblasts		Reduced number; impairment in biogenesis is not mediated by the PEX19-capsid interaction	PEX19 is not essential for peroxisomal targeting of ZIKV capsid		24, 48, 72 h	GST-pull down assay, confocal microscopy	[60]

[63] demonstrated a peroxisome density reduction and a decrease in PMP70 expression, both upon infection and transfection of the viral protein NS2A. Furthermore, PEX19 was reported not to be responsible for the decrease of peroxisome density in ZIKV infections [60]. The viral protein NS2A, which has been shown to localize at peroxisomes during ZIKV infection by interacting with PEX3 and PEX19, was suggested to be involved in peroxisome biogenesis dysfunction [63]. Similarly to DENV and WNV, ZIKV capsid protein interacts with PEX19, reducing its amount, as well as the amount of other peroxisomal proteins in infected cells [60, 62]: ZIKV capsid protein overexpression decreased PEX19 levels by 50%, and viral infection caused a reduction in PEX19, PEX3, PEX7, PEX11β, PEX13, and PMP70 levels [62]. The authors hypothesize that this downregulation of peroxisomal proteins may induce the impairment of IFNs production [60]. On the other hand, the reduction or loss of the peroxisomal proteins PEX19 or PEX3 has been shown to compromise viral infectivity and replication [59, 60, 62, 63]. Furthermore, higher peroxisome density due to overexpression of PEX11β impaired ZIKV replication, possibly via activation of the peroxisome-dependent immune response [62]. Interestingly, the serum of ZIKV-infected patients presents increased levels of plasmalogens [64].

Further experiments are needed to disclose the mechanisms involved in this interplay, as well as how these differ among the different phases of the virus life cycle: as it was previously discussed for HCMV, different levels of peroxisome modulation may occur at distinct infection stages.

2.7.4 Hepatitis C Virus (HCV)

HCV infection has been shown to induce an impairment of peroxisome metabolism and the intracellular accumulation of VLCFAs [65] (Table 12 and Fig. 1). As it was also found that VLCFA synthesis is crucial for HCV infection [66], further studies should analyze whether stimulation of peroxisomal β-oxidation would lead to an impairment of HCV infection.

HCV has been revealed to inhibit the peroxisome-dependent antiviral response. The viral protein complex NS3-4A is able to cleave MAVS at peroxisomes, mitochondria, and mitochondria-associated membranes (MAMs) and consequently inhibit downstream signaling [67–69]. NS3-4A has been shown to localize at peroxisomes even in the absence of MAVS and inhibit antiviral signaling with similar kinetics as at mitochondria [67].

Table 12
Overview of the current results and methodologies employed to study the modulation of peroxisomal mechanisms during infection by the hepatitis C virus (HCV)

Cells, tissues, and patients	Peroxisomal alteration upon infection		Other obs.	Infection timepoints	Methods used	Refs.
	Metabolism	Antiviral signaling				
Huh7.5.1, liver tissues from mice, patients	Impaired β-oxidation: VLCFAs intracellular accumulation			1, 2, 3, 4, 5, 6, 7, 8, 9, 10 d	Omics, RNAseq	[65]
Huh7.5			VLCFAs synthesis is required for viral replication and assembly	4 d	Plaque assay, luciferase levels	[66]
MEFs, Huh7		NS3-4A cleaves MAVS at peroxisomes		From 2 h30 to 24 h, 48, 72 h	Western blot, immunoprecipitation, RT-qPCR, confocal microscopy	[67, 68]

3 Conclusions

The results described above clearly demonstrate that peroxisomes play important roles in the context of viral infections. Viruses from different families and origins have been shown to modulate peroxisome biogenesis and metabolism to promote virus particle formation and propagation or counteract the cellular antiviral response. This interplay can even diverge throughout infection, adjusting to the different requirements of each phase of the virus life cycle (Fig. 1).

However, research in this field is still relatively incomplete. Most studies have not addressed all the individual phases of the virus life cycle, and some of the experimental approaches even make use of a set of cells displaying different stages of infection. This is likely the reason for some of the divergence between the results presented in different reports. As shown for HCMV, the only virus for which a complete spatial-temporal analysis was performed, a depletion in peroxisome numbers occurs early in infection to inhibit antiviral signaling, while the stimulation of peroxisome metabolism and biogenesis occurs in a later infection stage to support the formation of new virus particles. Although further research should be performed to confirm this assumption, it is tempting to hypothesize that this may occur during infection by other viruses from the same family and even by viruses from different families. The difference in tools, cell lines, and methodologies

used may also account for the observed variances among different studies. To obtain solid data and draw clear conclusions on the peroxisome-dependent mechanisms that are important for each viral infection, detailed studies with similar experimental approaches should be performed at several timepoints over a single and complete infection cycle. These studies may lead to the discovery of novel peroxisome-related cellular targets that can further be exploited for the development of host-directed specific and/or broad-spectrum antiviral therapeutics.

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