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Peroxisomes are underappreciated organelles hijacked by viruses

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Keywords

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Abstract

Peroxisomes are cellular organelles that are crucial for metabolism, stress response and healthy aging. They have recently come to be considered as important mediators of the immune response during viral infections. Consequently, various viruses target peroxisomes for the purpose of hijacking either their biogenesis or their functions, as a means of replicating efficiently, making this a compelling research area. Despite their known connections with mitochondria, which have been the object of considerable research on account of their role in the innate immune response, much less is known about peroxisomes in this context. This review explores the evolving understanding of the role of peroxisomes, highlighting recent findings on how they are exploited by viruses in order to modulate their replication cycle.

Peroxisomes at a glance

Peroxisomes (see Glossary) were first identified as « microbodies » by Johannes Rhodin in 1954, and subsequently more fully characterized by Christian de Duve and Pierre Baudhuin, in 1966 [1]. These organelles have principally been studied in yeasts, receiving much less attention in mammalian cells, despite their crucial role in cellular metabolism, and their multiple connections with the other cellular organelles [2]. Historically considered as metabolic organelles, they are now recognized as crucial players in cellular antiviral defense mechanisms. This topic has acquired significant importance in recent years, notably with global viral pandemics highlighting the need for novel antiviral strategies. Their role in viral infections is particularly relevant, as it connects with a growing understanding of how cellular organelles actively contribute to immune responses. Within this field, one major question which remains open relates to the precise manner in which peroxisomes interact with viruses and contribute to antiviral immunity. While their metabolic functions are now well understood, the specific roles they adopt in the presence of viral infections are still being studied. In 2010, a pivotal study unveiled that they serve as important signaling platforms for antiviral responses, by triggering an **interferon (IFN)**-independent signaling pathway that promotes the expression of **Interferon-Stimulated Genes (ISGs)** [3]. Although not recent, this discovery remains fundamental to our understanding of peroxisomal functions. In revealing their role beyond metabolism, it marked a pivotal shift in how these organelles are perceived. Moreover, more recent research has uncovered intricate mechanisms by which viruses target and subvert peroxisomal functions to evade host immune responses. This review explores the dual role of peroxisomes in viral infections, showing them as both defenders against viruses and targets of viral manipulation. It presents a comprehensive view of peroxisomes as complex organelles involved in viral pathogenesis and host defense, and combin insights from various studies.

Structure

Peroxisomes are small spherical organelles delimited by a single membrane, abundantly present in the cytoplasm of almost every eukaryotic cell, and varying in size from 0.2 to 1 μm depending on what stage of maturation they have attained [4]. These organelles do not possess their own genetic material, and therefore depend entirely on the genetic material present in the cell nucleus for the synthesis of their specific proteins. The peroxisomal membrane separates the cellular cytoplasm from the peroxisomal matrix, which encompasses an electron-dense crystallin core. This core harbors oxidative enzymes such as catalase and various oxidases involved in breaking down peroxides and long-chain fatty acid degradation, purine metabolism and lipid biosynthesis. At their surface, peroxisomes harbor the **Mitochondrial AntiViral Signaling protein (MAVS)**, which is a crucial actor in the innate immune response. This highlights the involvement of these organelles in the arsenal of cellular defense against pathogens [3].

Regulation

Peroxisomes exhibit the capacity to proliferate in response to specific signals. Their number and enzymatic activity are thus tightly regulated by a dynamic interplay between the generation of new peroxisomes, which can arise either through the division of pre-existing ones or through *de novo* biogenesis from the endoplasmic reticulum (ER), and their degradation. Their biogenesis depends on specific proteins, namely the **peroxins (PEXs)**, which allow the import of the enzymes necessary for their functions (**Box 1**), and whose transcription is mainly controlled by the peroxisome proliferator-activated receptor α (PPAR α) transcription factor, as reviewed in [5]. At present, it remains unclear whether or not the other types of PPAR (β or γ) are associated to peroxisome proliferation.

In addition to their role in biogenesis, peroxisomes degradation is also pivotal for maintaining cellular homeostasis, overseeing both their abundance and functionality. Three mechanisms of peroxisome degradation have been identified: (i) the Lon protease system, which takes place within peroxisomes to degrade excess or damaged proteins, thereby contributing to the degradation of these organelles [6]; (ii) autolysis, where the 15-lipoxygenase oxidizes peroxisomal membrane lipids, leading to peroxisome fragmentation and subsequent degradation [7]; and (iii) **pexophagy**, which is the main process regulating

the peroxisomes number and, thus, their function [8]. Pexophagy is the selective degradation of peroxisomes by autophagy, and appears to be the most critical mechanism for disposing of impaired or excess peroxisomes. Indeed, one study has revealed that the conditional knock-out of ATG7, an essential autophagy protein, leads to a 70 to 80% of excess peroxisomes in mice [9] (**Box 2**). This phenomenon has also been confirmed in the context of HIV-1 infection. Indeed, the downregulation of p62/SQSTM1 or BECLIN 1 expressions, two key autophagy proteins, prevents the degradation of PEX14 in virus targeted cells. This finding underscores the significant role played by autophagy in the degradation of peroxisomes in the context of viral infection [10].

Functions

Peroxisomes fulfill various crucial functions in lipid metabolism, and are major players in the cell redox balance maintenance. In mammals, they actively participate in various metabolic processes, including fatty acid β -oxidation and the synthesis of bile acids and **plasmalogens**, while also regulating innate immune and redox signaling pathways [11]. The proper functioning of peroxisomes is vital for human development, with their dysfunction being linked to severe genetic disorders such as the **Zellweger syndrome**. The metabolic functions of these organelles are mediated by enzymes within the peroxisomal matrix, which includes more than 100 different proteins [11,12]. Peroxisomes interact with **mitochondria** and the ER as a means of coordinating their metabolic functions and maintaining cellular homeostasis, forming a “redox triangle” crucial for regulating oxidative balance (Figure 1) [2,13]. These organelles are closely associated through membrane contact sites, allowing them to work together in generating and regulating the quantity of **reactive oxygen species** (ROS), particularly hydrogen peroxide (H_2O_2). Specialized enzyme complexes, known as “redoxosomes”, are formed within this triangle and serve as sensors for ROS accumulation, facilitating signaling between organelles by means of the modification of proteins and lipids [13]. Within the redox triangle, peroxisomes play a crucial role in producing and detoxifying ROS, enhancing inter-organelle communication and contributing to cellular redox balance through their involvement in the formation of “redoxosomes” and in lipid metabolism.

While the function of peroxisomes in the context of viral infection has been the object of much less study, it has nonetheless retained the attention of researchers over the past decade because several viruses have been shown to target these organelles during their replication cycle. Indeed, it has been demonstrated that, like mitochondria, they harbor MAVS, which is a crucial mediator of the innate immunity [3]. Upon viral entry into their target cells, viral nucleic acids are sensed by a family of proteins known as the **RIG-I Like Receptors (RLRs)**. Within this family, Retinoic Acid-Inducible Gene-I (RIG-I) and Melanoma Differentiation-Associated protein 5 (MDA5) act as primary sensors that activate MAVS located on both mitochondria and peroxisomes membranes [14], as well as on a subdomain of the ER called the **mitochondria-associated membrane (MAM)** [15]. Activated MAVS serves as a molecular platform for the assembly of signaling complexes, which in turn triggers downstream antiviral signaling cascades (**Figure 2**). These include the induction of type I and type III interferons (IFNs), which are key antiviral cytokines, as well as pro-inflammatory cytokines. It has been demonstrated that peroxisomal and mitochondrial MAVS act sequentially in this context [3,16]. Peroxisomal MAVS initiate a rapid induction of IFN-stimulated genes (ISGs) independently of IFN production. This response relies on the transcription factors IRF1 (IFN Response Factor 1) and IRF3. IRF1 is a constitutive transcription factor known for its role in short-term protection against pathogens [17,18]. In contrast, mitochondrial MAVS only activates IRF3, which subsequently triggers the production of type I IFN, responsible for the amplification and stabilization of the antiviral response. It has been shown that, as a consequence, the cross-talks between peroxisomes and other cellular organelles, such as mitochondria, amplify the antiviral signaling pathways and coordinate the cellular responses to viral infection [3]. The mechanisms of viral recognition and response must be understood if the role of peroxisomes in antiviral defense is to be elucidated. These underappreciated functions are more thoroughly examined in the following chapter.

Peroxisomes during viral infections

As obligate intracellular parasites, viruses co-evolve with their hosts and develop various strategies to ensure their replication and dissemination. The literature is full of examples of how viruses hijack the cellular machinery and inhibit the antiviral response. In the past, the involvement of peroxisomes in this context has

been relatively underappreciated, but an increasing number of studies have begun to shed light on significant interactions between these organelles and a variety of viruses [19,20]. Indeed, because of their function and composition, peroxisomes are prime targets for viral manipulation. In the following chapters, we will describe three primary modes of action used by viruses to ensure a successful life cycle through their interaction with peroxisomes. It should be noted that these modes of action are intimately interconnected, given that insofar as any action which affects one mode can have consequences on the others.

Viruses affecting peroxisome dynamics

Depending on viruses, peroxisomes biogenesis can be either inhibited or stimulated during infection. For example, HIV-1 (Human Immunodeficiency Virus type 1) is able to downregulate the expression of genes involved in peroxisome biogenesis, such as *Pex2*, *Pex7*, *Pex11 β* , and *Pex13* [21]. This downregulation is due to a viral-mediated induction of specific microRNAs (miRNAs), leading to the reduction of the relative peroxisomal transcripts expression levels. Furthermore, in a following study, the authors demonstrated that the expression of these miRNAs is induced by the HIV-encoded auxiliary protein Vpu [22]. Specifically, Vpu stabilizes β -catenin, which then activates miRNA promoters and inhibits the translation of the peroxisome biogenesis factors [14]. Paradoxically, some HIV-1-induced miRNAs that target PEX mRNAs may also enhance the expression of innate immune genes [21]. Currently, there is limited knowledge regarding aberrant miRNAs expression and its impact on peroxisomal biogenesis disorders. Future studies will be needed to elucidate how viruses manipulate miRNAs to uncover their roles in peroxisome-dependent antiviral defense mechanisms. In the same way, flaviviruses, such as West Nile Virus (WNV), Zika virus (ZIKV) or Dengue Virus (DENV), are known to reduce the number of peroxisomes, ultimately diminishing their antiviral effect because of their massive loss. Indeed, WNV and DENV capsid proteins has been shown to sequester and induce the degradation of the peroxisome biogenesis factor PEX19 [23]. Similarly, ZIKV virus capsid protein harbors a PEX19 binding motif and forms a stable complex with this protein, leading to a decrease in peroxisome numbers and PEX19 expression [24]. Last but not least, enterovirus 71 disrupts peroxisomes by downregulating ACOX1 (acyl-CoA oxidase 1) and PEX19, resulting in a decrease in peroxisome numbers and in a subsequent accumulation of ROS [25]. The elevated ROS levels trigger both neural cell apoptosis and autophagy, underscoring the critical role of peroxisomes in maintaining cellular redox homeostasis, particularly in the central nervous system (CNS). Peroxisomal dysfunction is also a hallmark of many neurodegenerative diseases, which are linked to neuroinflammation [26]. While redox imbalance has been extensively studied in the context of viral infections and neurodegenerative diseases, the primary focus has been made on mitochondrial dysfunction, with much less attention given on peroxisomes [27]. It is therefore tempting to speculate that in neurotropic viral infections, disturbances in peroxisomal dynamics could further exacerbate oxidative stress, contributing to neuronal damage and possibly accelerating the progression of neurodegenerative processes.

In an opposite manner, Herpesviruses, such as Human CytoMegalovirus (HCMV), Kaposi's Sarcoma-associated Herpes Virus (KSHV), Epstein-Barr Virus (EBV) and Herpes Simplex Virus 1 (HSV-1), are able to stimulate peroxisomes biogenesis in order to favor their replication. Specifically, in this context it was discovered that HCMV and HSV-1 induce the biogenesis and unique morphological changes of peroxisomes to support their replication [28,29]. This peroxisome regulation was not observed for adenovirus, which is a non-enveloped virus, suggesting that the use of these organelles for viral benefit is not a conserved mechanism among viruses [29]. In particular, HCMV is able to upregulate the expression of several PEXs involved in metabolic and signaling pathways, such as PEX3, PEX14 and **Peroxisomal Membrane Protein 70** (PMP70), among other examples. This upregulation contributes to the remodeling of peroxisomal membranes, the enhancement of lipid metabolism, and the modulation of ROS levels. Likewise, latently KSHV-infected cells present an increased number of peroxisomes, suggesting a crucial role for these organelles in supporting viral latency and persistence [30]. This hypothesis is further supported by the increased expression of proteins involved in peroxisomal lipid metabolism, such as PMP70 and ACOX1, which have been identified as critical for the survival of KSHV-latently infected cells. Thus, it seems possible that, by increasing the number of peroxisomes and by modulating the expression of proteins involved in peroxisomal lipid metabolism, KSHV creates a favorable cellular environment for viral latency and persistence. EBV can also manipulate peroxisomes by regulating the expression of various proteins involved in their biogenesis, lipid degradation, and antioxidant mechanisms. Specifically, an increase in PEX19 during

the acute phases of EBV infection, as well as in EBV-transformed cells, has been observed [31]. Previous research has shown that other herpesviruses such as KSHV and HCMV use PEX19 to anchor specific viral proteins (vFLIP [32] and vMIA [28], respectively) to peroxisomes to establish latency. It would therefore be interesting to investigate if EBV also modulates PEX19 expression through direct interaction, akin to these aforementioned viruses. Although they are all herpesviruses, it is noteworthy that they interact with peroxisomes through distinct mechanisms to manipulate peroxisome biogenesis and to enhance their own replication processes.

Beside affecting peroxisomal biogenesis, to date HIV-1 is the only virus known to directly induce peroxisome degradation. Indeed, HIV-1 envelope glycoproteins (Env), expressed at the surface of infected cells, induce pexophagy (**Box 2**) in bystander uninfected CD4+ T lymphocytes [10]. This Env-induced pexophagy results in an excessive oxidative stress, leading to apoptotic cell death. This discovery highlights the virus's ability to influence both peroxisome biogenesis and degradation throughout its life cycle. Modulating the number of peroxisomes can thus indirectly impact their overall effectiveness in cellular processes. Reducing peroxisome levels helps viruses evade the host's antiviral defenses, disrupts lipid metabolism, and increases oxidative stress, thereby facilitating viral replication. Increasing peroxisomes, on the other hand, may enhance metabolic processes, reduce oxidative damage, and disrupt the host's immune response, all of which support viral persistence and replication. These contrasting strategies highlight the evolutionary adaptations of different viral families in response to host cell defenses and their specific replication needs. Any full understanding of virus-host interactions must therefore take into account viruses' ability to modulate peroxisome numbers. That ability places these organelles alongside other key cellular structures, such as the ER, the Golgi apparatus, and the mitochondria, in the context of viral manipulation. Additionally, peroxisomal function can be directly targeted by the virus, a topic that will be detailed in the following section. The capacity of viruses to modulate PPAR α remains largely unexplored, even if recent studies have indicated that certain viruses, such as SARS-CoV-2 and Hepatitis C Virus (HCV), can influence this transcription factor [33,34]. PPAR α regulates the expression of PEX proteins which are crucial for peroxisome biogenesis. This viral manipulation suggests that targeting PPAR α and, more broadly, the peroxisomal pathways, could be a promising antiviral strategy. Rather than targeting viruses directly, modulating PPAR α to influence peroxisomal activity could be a new therapeutic approach with broad-spectrum potential, especially given that peroxisome dynamics are critical for the progression of several viral infections. More generally, it should be noted that PPARs are key regulators of lipid metabolism, inflammation, and immune responses, and that PPAR modulators are already used clinically to treat a range of metabolic and inflammatory diseases [35]. The development of PPAR agonists has further enhanced therapeutic potential, making it an adaptable approach applicable to complex diseases. Repurposing PPAR modulators for antiviral therapies could potentially disrupt viral replication and boost antiviral immune responses, positioning PPARs as a versatile target for future antiviral drug development. Leveraging PPARs for broad-spectrum antiviral strategies could lead to treatments that are effective against multiple viral infections, by modulating host pathways rather than targeting viruses.

Viruses using peroxisome functions for their replication

In addition to modulating peroxisome dynamics, some viruses can directly hijack peroxisomal functions to promote their own replication. For example, the structural protein VP4 of rotavirus SA11 localizes to peroxisomes *via* a conserved peroxisomal targeting signal 1 (PTS1) domain, indicating that rotaviruses may exploit peroxisomes to promote their replication, although the precise mechanism of this process remains unclear [36,37]. Similarly, the rise in peroxisome numbers which is triggered by HCMV, as discussed earlier, correlates with a metabolic boost that enhances the production of plasmalogens and very long chain fatty acid, crucial for the viral lifecycle [29,38]. Peroxisomes are also essential for the replication of *Flaviviridae*, particularly in facilitating efficient ZIKV replication [39]. In this context, the viral NS2A protein targets peroxisomal membranes by interacting with PEX3 and PEX19, potentially reducing peroxisome numbers through host-cell lipid remodeling. While PEX3 and PEX19 are not directly involved in lipid remodeling, their crucial roles in peroxisome biogenesis and maintenance significantly influence the host cell's overall lipid metabolism. Disruptions to their function can cause substantial changes in the cellular lipid profile [40], resulting in the potential promotion of viral replication or assembly. Additionally, both WNV and ZIKV manipulate peroxisomal lipid metabolism during infection. WNV infection boosts cellular

glycerophospholipids, including plasmalogens and sphingolipids, while ZIKV infection raises plasmalogen levels in patient serum [41,42]. It appears likely that this manipulation supports membrane remodeling and viral vesicle formation, which are crucial for their infection cycles. Another study on HCV showed that peroxisomes are relocated in close proximity to viral-induced replication complexes [43]. That study also observed increased ROS levels and reduced catalase activity, specifically in peroxisomes of HCV replicon-containing cells, indicating an impaired redox balance. This observation aligns with previous research which demonstrated that persistent HCV infection disrupts peroxisome function, lipid metabolism, and pathways related to fatty acids and bile acids [44]. Finally, other studies have highlighted the role of peroxisomes in the replication of respiratory viruses. Specifically, a lipodomic study revealed that phosphatidylcholines synthesized within peroxisomes contribute to the composition of the Influenza virus envelope, potentially influencing viral entry, replication, and assembly processes [45]. Furthermore, similar to HCV, an accumulation of peroxisomes near viral-induced double membrane vesicles, which serve as sites for viral replication, has been observed during SARS-CoV-2 infection, in a manner which suggests a protective role of these organelles against oxidative damage. In the same infectious context, another hypothesis is that the virus could exploit peroxisome-mediated lipid metabolism to enhance viral replication [46]. Additionally, SARS-CoV-2 infection results in the reorganization of the peroxisomal membrane, compromising its integrity and reducing the number of functional peroxisomes [47]. However, the full implications of this process remain unknown. These viral subversions of peroxisome functions allow viruses to benefit from the energetic resources of the host cell but also to evade cellular defenses.

Viruses targeting peroxisomes to impact the immune response

The crucial role of peroxisomes as signaling platforms in RLR-mediated antiviral immunity has been established, highlighting both the similarities to and differences from mitochondria. Numerous studies have shown that many viruses trigger an innate immune response, such as IFNs and ISGs synthesis, through peroxisomal MAVS signaling [48,49]. However, there also exist many examples that demonstrate the specific evasion of peroxisome-dependent signaling by various pathogenic viruses (see **Table 1**). These manipulations enable them to bypass early viral detection and allow them to evade any effective and rapid immune response. Among these viruses, Herpesviruses remain the most extensively studied family. HSV-1 has been shown to block peroxisomal MAVS-mediated early ISGs production through its VP16 protein, dampening the immediate early antiviral innate immunity signaling which is supported by peroxisomes [50]. HCMV can specifically evade the peroxisome-mediated antiviral response by using its anti-apoptotic protein vMIA, which interacts with peroxisomal MAVS, inhibiting their oligomerization, thereby restraining downstream immune signaling [51]. It should be noted that this virus also targets mitochondrial MAVS through a completely different mechanism, reflecting the intrinsic differences and roles of these organelles during viral infection [51]. While other Herpesviruses evade host antiviral responses by impairing MAVS function, KSHV uses peroxisomal MAVS to sustain viral infection. More precisely, vFLIP, a viral oncoprotein crucial for KSHV survival, localizes at peroxisomes in a PEX19-dependent manner [32]. At the peroxisome, vFLIP is stabilized by MAVS, and this process is essential for establishing KSHV latency. Concerning other virus families, HCV NS3/4A serine protease has been shown to cleave MAVS, from both mitochondria and peroxisomes, to inhibit IFN synthesis [52,53]. This viral protein localizes to peroxisomes even in the absence of MAVS, although MAVS presence stabilizes NS3/4A on this organelle. As a result, the weakened innate immune response allows HCV to go undetected and to proliferate in host liver cells, potentially facilitating the establishment of persistent infection.

Finally, HIV-1-encoded Nef interacts with peroxisomal thioesterase ACOT8, leading to the downregulation of the expression of both its cellular receptor CD4 and of the major histocompatibility complex (MHC) class I in infected cells [54,55]. This interaction is thought to interfere with both antigen presentation and T cell activation, highlighting an unusual, peroxisome-related immune evasion strategy.

Several other viruses evade the IFN response by directly targeting MAVS. These include coxsackievirus B3 and enterovirus 71, both of which use their specific viral proteases to cleave MAVS. While the studies in this chapter focus primarily on mitochondrial MAVS, it would be intriguing to investigate whether this cleavage might also occur at the surface of peroxisomes. Such exploration could shed light on the role of peroxisomes in other viral infections. Indeed, all such speculation highlights the need for further research on peroxisome-dependent signaling in the context of viral infection. Specific experimental methodologies are thus essential,

given MAVS's native localization across both organelles. Readers are encouraged to consult the book chapter titled "Tools to Investigate the Peroxisome-Dependent Antiviral Response" [56], where specific methods by which this promising area of research are detailed.

Concluding remarks

Peroxisomes have long been studied only for their essential role in cellular metabolism. However, several viruses have now been identified which target these organelles in order to replicate more efficiently, and in doing highlight the organelles' contributions to host defense against viral infection. Viruses target peroxisomes in multiple ways: they can affect the peroxisomes' biogenesis, or can modulate or indeed hijack their functions, and in doing so circumvent peroxisomes' role in the innate immune response. This last point is confirmed by the fact that peroxisomes harbor MAVS at their surface, a phenomenon indicative of their underestimated role in the innate immune response. MAVS was initially identified as a protein located to mitochondria and their associated membranes issued from the ER, where its role in the innate immune response is performed [57]. As discussed earlier, MAVS distinct localization may drive diverse antiviral signaling programs. It would appear that both MAVS located on peroxisomes and mitochondria provide a coordinated and complementary response to viral infection. Specifically, peroxisomal MAVS are responsible for a rapid protection action through the induction of antiviral proteins, doing so without the need for antiviral cytokines secretion. Mitochondrial MAVS, for their part, act in a second time to reinforce this protection by inducing type I IFNs and pro-inflammatory cytokines [3]. A deeper exploration of this model would define the peroxisome as a key player in intrinsic immunity, insofar as the peroxisomal response directly and swiftly restricts viral replication without requiring intermediary molecules such as IFN. These distinct roles of MAVS, which vary according to its localization, have yet to be fully elucidated and as such require further investigation. In this regard, a recent study has demonstrated that differential localization of MAVS also directs different glucose metabolic pathways, indicating that MAVS integrates both glucose metabolism and RIG-I-like receptor signaling [58]. It might be speculated that this dual role is the key to explaining, at least in part, the MAVS signaling differences which vary according to their localization. However, given the extensive physical and functional interactions among peroxisomes, mitochondria and the ER [2], it is plausible that MAVS localization does not exclusively dictate organelle-specific functions. Instead, its antiviral signalization likely represents an integrated response within a larger signaling hub, as supported by the notion of a "redox triangle", wherein ER-mitochondria-peroxisome generates a multi-organellar protein complex called the "redoxosome" [13]. The existence of such a super-organelle would reconcile the concepts of innate and intrinsic immunity, insofar as it would link them physically, functionally, and temporally (see **Outstanding questions**).

The role of mitophagy (selective degradation of mitochondria by autophagy) in the context of viral infection has been extensively studied while the role of pexophagy remains fragmentary. This being the case, future studies should be conducted in order to discriminate the role of each organelle during viral infection. Specifically, research into virus-mediated pexophagy and mitophagy could deepen our understanding of each pathway and, more generally, provide better knowledge of selective autophagy processes and cellular pathways. Finally, there is much that might be learned from a deeper investigation of the interplay of cellular organelles, including ER, lysosomes and lipid droplets, in the context of viral infection, given the considerable synergy and contact sites they share. Such research would also be an opportunity to investigate the possible impact of their metabolic connections on cellular antiviral response.

Understanding the molecular mechanisms of viruses and peroxisomes interactions would therefore appear essential to the development of new therapeutic strategies which could enhance the immune response against viral infection. As such, this represents a fascinating and promising area of research in the fight against viral disease.

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Declaration of interests

The authors declare no competing interests.

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Glossary

Interferon (IFN): protein of the immune system that helps fight infections by inhibiting viruses and activating other immune defenses.

Interferon Stimulated Gene (ISGs): genes activated by interferons to help combat infections by producing proteins that inhibit viruses and enhance immune responses.

Mitochondrial AntiViral Signaling (MAVS): crucial component of innate antiviral immunity, located in the outer membrane of mitochondria, mitochondria-associated membrane and peroxisomes.

Mitochondria: organelle that produces energy for the cell and helps trigger innate immune responses.

Mitochondria-associated membrane (MAM): specialized regions where the endoplasmic reticulum and mitochondria interact, facilitating the exchange of lipids, calcium, and signaling molecules. They play crucial roles in cellular processes such as calcium signaling, lipid metabolism, and apoptosis regulation.

Peroxin (PEX): family of proteins involved in peroxisome biogenesis.

Peroxisome: organelle involved in cell detoxification, fatty acid metabolism and innate immunity.

Pexophagy: a type of selective autophagy where peroxisomes are specifically degraded by the lysosome, involving their sequestration within double-membrane vacuoles called autophagosomes.

Plasmalogens: type of phospholipid in cell membranes that protect cells from oxidative stress and are involved in cell signaling and membrane fluidity.

Peroxisomal Membrane Proteins (PMPs): proteins located in the membrane of peroxisomes that are involved in peroxisome biogenesis, maintenance, and function.

Peroxisome Targeting Signal (PTS): specific sequence of amino acids that targets proteins to be imported into peroxisomes.

RIG-I-Like Receptors (RLRs): key sensors of virus infection ultimately leading to the induction of an antiviral response.

Reactive oxygen species (ROS): reactive oxygen-containing molecules generated during cellular metabolism, influencing both cell signaling and oxidative stress.

Zellweger syndrome: peroxisomal biogenesis disorder which results from mutations in PEX genes (leading to dysfunctional peroxisome assembly and impaired metabolism of long-chain fatty acids), causing

severe neuronal and developmental abnormalities.

Elements

BOX 1: Peroxisomal biogenesis

Peroxisome biogenesis relies on two co-existing pathways: (i) growth and division of pre-existing peroxisomes, or (ii) "*de novo*" synthesis of peroxisomes from the endoplasmic reticulum (ER). In the first pathway, pre-existing peroxisomes undergo remodeling, elongation, and eventual division, akin to the processes observed for mitochondria [59,60]. Initially, peroxisomal membrane remodeling and expansion occurs through the development of tubular extensions, facilitated by the import of **Peroxisomal Membrane Proteins (PMPs)** and lipids from the ER. This process often takes place at membrane contact sites between the ER and peroxisomes [2,61,62], or *via* fusion with pre-peroxisomal vesicles. The regulation of this dynamic process in mammals involves various proteins, among which **peroxin 11 β** (PEX11 β) is the most notable [63]. PEX11 β not only regulates peroxisome proliferation but also facilitates the assembly of the fission machinery by interacting with key components, such as FIS1, MFF, and DRP1 [64–67]. This interaction ultimately induces membrane constriction and subsequent fission, leading to the formation of new peroxisomes [68]. New peroxisomes are not only synthesized from pre-existing ones. They can also emerge *de novo*. During this process, which is still poorly characterized in mammals, the peroxisome biogenesis begins with the proliferation of a specialized structure known as a « pre-peroxisome » from the ER membrane, instigated by proteins such as PEX16 [69–72]. PEX16 is a key player in recruiting various PMPs to the ER, including PEX3 and members of the PEX11 family [73], thereby promoting the formation and budding of pre-peroxisomal vesicles. Once released from the ER, these vesicles undergo maturation into functional peroxisomes through the import of (i) PMPs, *via* the action of the PEX3-PEX19 complex [74,75], and (ii) peroxisomal matrix proteins from the cytosol, through PEX13, PEX5 and PEX7, which serve as receptors for proteins with **Peroxisome Targeting Signals (PTS1 and PTS2)** [76,77]. Additionally, recent investigations have suggested that newly synthesized peroxisomes may result from the fusion of two distinct populations of pre-peroxisomal vesicles, one originating from the ER and the other from mitochondria, thus highlighting the interconnected nature of these cellular organelles [78].

BOX 2: Pexophagy

Pexophagy is the selective degradation of peroxisomes by autophagy, which is a ubiquitous lysosomal degradation pathway [73]. At the basal level, autophagy allows the recycling of cellular components, but it can also be induced under stress conditions such as viral infection. Autophagy is characterized by the formation of double-membrane vesicles, the autophagosomes, which sequester material which will subsequently be degraded, after their fusion with lysosomes [79]. Among the complexes regulating autophagy, two ubiquitin-like conjugation systems are involved in the covalent binding of ATG8/LC3B proteins to phosphatidylethanolamine (PE) residues which are present on the developing autophagosomal membranes. The selectivity of autophagic degradation relies on the so-called autophagic receptors (ARs), amongst which the SLRs (sequestosome 1 like-receptors) are able to simultaneously interact with targeted cargoes and with the ATG8/LC3B proteins which are anchored on autophagosomal membranes, thereby physically linking the substrate with the autophagosome [80]. Substrates are often ubiquitinated and therefore recognized by the ubiquitin-binding domain (UBA) present on most ARs. However, ubiquitin-independent mechanisms have also been identified. Extensively studied in yeast [81], pexophagy has received less attention in mammalian models [82]. While ubiquitin-dependent mechanisms of pexophagy are now being more fully characterized, the identification of non-ubiquitin dependent pathways underscores the diversity of regulations involved in this crucial autophagic process.

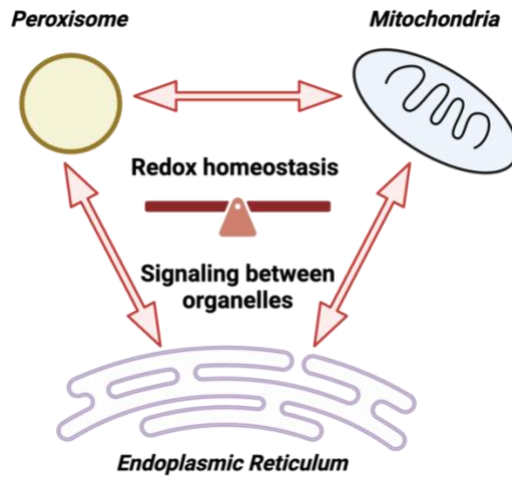


Figure 1: “Redox triangle”, an enhancer of peroxisome function

Peroxisomes, mitochondria, and the endoplasmic reticulum (ER) form a dynamic “redox triangle” through specialized membrane contact sites, allowing coordinated regulation of metabolism and reactive oxygen species (ROS) production. This interconnected network is essential for maintaining cellular redox homeostasis and balancing oxidative processes.

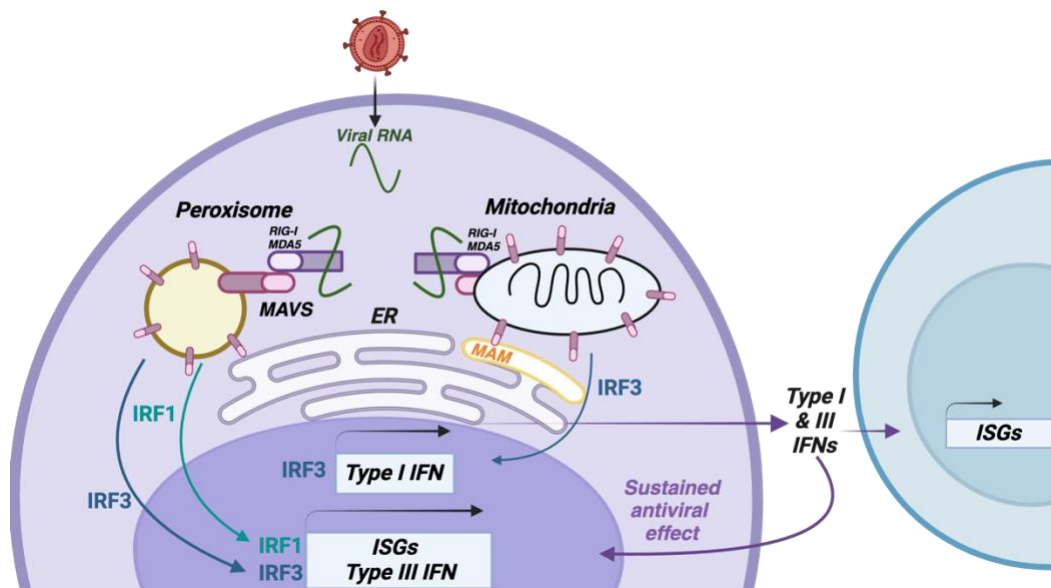


Figure 2: Coordinated antiviral response mediated by peroxisomal and mitochondrial MAVS

Upon viral RNA detection in the cytoplasm, Pattern Recognition Receptors (PRRs), such as RIG-I and MDA5, are activated and bind to the Mitochondrial Antiviral Signaling protein (MAVS) present on both peroxisomes and mitochondria, including on Mitochondria-Associated Membranes (MAMs), which are a subdomain of the Endoplasmic Reticulum (ER).

First, peroxisomal MAVS are activated rapidly after viral entry, activating Interferon Regulatory Factors 1 and 3 (IRF1 and IRF3). These factors stimulate the expression of Interferon-Stimulated Genes (ISGs), providing an immediate antiviral protection and promoting type III interferon (IFN) production and secretion. Subsequently, mitochondrial MAVS trigger a signaling cascade that specifically activates IRF3, leading to its nuclear translocation and the induction of type I IFN expression. The newly secreted type I and type III IFNs act through autocrine and paracrine mechanisms, amplifying ISGs expression and establishing a broad antiviral response. This intricate interplay between cellular structures, signaling proteins and gene regulators facilitates a redox-sensitive immune response to viral RNAs, enabling sustained antiviral protection.

Table 1. Multiple virus strategies to hijack peroxisomes

	Virus	Viral protein involved	Mechanisms	References
Viruses acting on peroxisome dynamics	<i>HIV-1</i>	<i>Vpu</i>	Downregulates genes involved in peroxisome biogenesis due to induction of specific microRNAs	[21,22]
		<i>Env</i>	Triggers pexophagy leading to oxidative stress	[10]
	<i>WNV, ZIKV and DENV</i>	<i>Capsid proteins</i>	Sequester and induce degradation of PEX19, reducing peroxisome numbers	[23,24]
	<i>Enterovirus 71</i>	/	Downregulates ACOX1 and PEX19, leading to a decrease in peroxisome numbers Accumulation of ROS	[25]
	<i>HCMV, HSV-1</i>	/	Induces biogenesis and morphological change in peroxisomes Upregulates PEXs	[28,29]
	<i>EBV</i>	/	Regulates expression of proteins involved in peroxisome biogenesis, lipid degradation, and antioxidant mechanisms	[31]
	<i>HCMV, KSHV</i>	vFLIP (for KSHV) and vMIA (for HCMV)	Use PEX19 to anchor vFLIP to peroxisomes for establishing latency	[28,30,32]
	<i>SARS-CoV-2, HCV</i>	/	Modulation of PPAR α	[33,34]
Viruses using peroxisome functions for their replication	<i>Rotavirus</i>	<i>VP4</i>	Exploits peroxisome via a mechanism that is still unclear	[28]
	<i>HCMV</i>	/	Induces a metabolic boost: production of plasmalogens and very long chain fatty acids	[29,38]
	<i>ZIKV</i>	<i>NS2A</i>	Targets peroxisomal membranes, potentially reducing peroxisome numbers through host-cell lipid remodeling. Raises plasmalogen levels in patient serum.	[39,42]
	<i>WNV</i>	/	Manipulates peroxisomal lipid metabolism Boosts cellular glycerophospholipids, including plasmalogens and sphingolipids	[41]
	<i>HCV</i>	/	Relocates peroxisomes near viral replication complexes, increases ROS levels, and reduces catalase activity Disrupts peroxisome function and lipid metabolism	[43,44]
	<i>Influenza Virus</i>	/	Exploits peroxisomes to contribute to the composition of the viral envelope	[45]
	<i>SARS-CoV-2</i>	/	Accumulates peroxisomes near double membrane vesicles Reorganizes peroxisomal membrane, compromising integrity and reducing functional peroxisomes	[46,47]
Viruses targeting peroxisome to impact the innate immune response	<i>HSV-1</i>	<i>VP16</i>	Blocks peroxisomal MAVS-mediated early ISGs production	[50]
	<i>HCMV</i>	<i>vMIA</i>	Inhibits MAVS oligomerization, thereby restraining downstream signaling	[51]
	<i>KSHV</i>	<i>vFLIP</i>	Utilizes peroxisomal MAVS to establish latency	[32]
	<i>HCV</i>	<i>NS3/4A</i>	Cleaves MAVS to inhibit IFN synthesis	[52,53]
	<i>HIV-1</i>	<i>Nef</i>	Interacts with ACOT8 and downregulates the expression of CD4 and MHC class I	[54,55]