Intracellular Organelles

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Viruses have evolved different strategies to hijack subcellular organelles during their life cycle to produce robust infectious progeny. Successful viral reproduction requires the precise assembly of progeny virions from viral genomes, structural proteins, and membrane components. Such spatial and temporal separation of assembly reactions depends on accurate coordination among intracellular compartmentalization in multiple organelles. Virus trigger the rearrangement and morphology remodeling of intracellular organelles, including the quality control of intracellular organelles, the hijacking of the modified organelle membranes, morphology remodeling for viral replication, and degradation of intracellular organelles by virus-triggered selective autophagy.

virus intracellular organelles rearrangement remodeling

1. Introduction

To maximize their viral replication and evade host antiviral responses**,** viruses have evolved a plethora of strategies to hijack cellular organelles [1][2][3]. Each step of viral replication is closely accompanied by the rearrangement of intracellular organelles.

2. Remodeling of the mitochondria for viral replication

The mitochondria are highly dynamic organelles and form interconnected tubular networks, undergoing a balance between fusion and fission in response to intracellular and/or extracellular stresses [4] (Figures 1A and 1B). Mitochondrial fusion involves two sets of key GTPase proteins in mammals: the mitofusin GTPases (Mfns) (Mfn1 and Mfn2) of the outer mitochondrial membrane (OMM) and optic atrophy 1 (OPA1) of the inner mitochondrial membrane (IMM) [5][6][7][8][9]. The Mfns mediate OMM fusion and cristae integrity [10]. However, the OPA1 mediates IMM fusion and cristae integrity by regulating of the mRNA splicing forms, membrane potential, and the adenosine triphosphate (ATP)-dependent diverse cellular proteases [6][7][8]. Subsequently, OMM fusions are followed by IMM fusion processes, resulting in the concomitant mixing of the mitochondrial contents and merging of two individual mitochondria. In a previous study, Cipolat, S et al. identified that OPA1 specific functional cross-talk with Mfn1 rather than Mfn2 is involved in the mitochondrial fusion of OMM [11]. Mitochondrial fission is a complex process which includes two distinct steps: an initial constriction of mitochondrial membranes and membrane scission. The initial constriction step narrows the mitochondrial tube diameter at the ER-mitochondria intersection zones where ER tubules wrap around the OMM. Manor, U. et al. suggested that actin-nucleating protein spire 1C localizes to the mitochondria, and directly links the mitochondria to the actin cytoskeleton and the ER, and finally promotes actin polymerization at the ER-mitochondria intersections [12]. The membrane scission of the mitochondria is primarily

regulated by dynamic relative GTPase protein (DRP-1) [13]. The mitochondrial localization of DRP-1 is a cytosolic factor promoting mitochondrial fission, which powers the constriction and division of the mitochondria primarily through post-translational modification (e.g., phosphorylation) (reviewed by Lee. H et al. [14]). Recent studies have reported that the recruitment of DRP-1 in mammalian cells requires several accessory proteins, such as the mitochondrial fission protein 1 (Fis-1) and mitochondrial fission factor (Mff) [15]. Although such proteins are proposed to constitute the fission complex of the mitochondria, mediating mitochondrial fission using this complex has remained unclear.

Viruses have evolved several strategies to remodel the mitochondria for viral replication and assembly, including spatial distribution, morphology remodeling, and metabolism reprogramming. To maximize the effectiveness of DNA replication, African swine fever virus (ASFV) infection recruits the mitochondria around the viral factories, associated with the morphology change and accumulation of the mitochondria. It was speculated that the translation and ATP synthesis are coupled and compartmentalized around viral factories to promote virus replication [16] (Figure 1C). Normal mitochondria are dynamic organelles, and form interconnected tubular networks [4][17] (Figure 1A). The cristae remodeling of the IMM determines the assembly and stability of respiratory chain supercomplexes and respiratory efficiency [18]. In general, the mitochondrial elongation process is associated with the dimerization and activation of the ATPase function to produce additional energy [17][19]. NDV induces the hyper-fusion of the mitochondria in infected A549 cells (unpublished data), which is similar to the characteristic of Dengue virus (DENV) [20] and severe acute respiratory syndrome-coronavirus (SARS-CoVs) [21]. Notably, except for vaccinia virus (VV) [22], most viruses exploit aerobic glycolysis of the mitochondria for the production of viral progeny [2].

Moreover, viral infections may increase the inter-organellar interactions of the mitochondria with other organelles for replication. Rubella virus (RUBV) [23] and Bunyamwera virus (BUNV) [24] infections increase the membrane interactions among mitochondria, ER, and Golgi (Figure 1C), which is consistent with that of the ER-mitochondria contract that serves as a platform for inter-organellar communication [25].

Figure 1. Morphology remodeling and spatial redistribution of mitochondria triggered by virus infections. (**A**) The morphological diagram of the mitochondria. Mitochondria form a dynamic network pool, which constantly undergoes rearrangement and turnover. The equilibrium regulation of mitochondrial fusion–fission is essential to maintain the integrity of mitochondria [26]. The morphology of mitochondria was divided into hyper-fused (elongated), tubular (normal), short tubes, and fragmented [17]. (**B**) Regulation of mitochondrial fusion and fission. Mitochondrial fusion is mediated by mitofusin GTPases MFN1 and MFN2 at the outer mitochondrial membrane (OMM), and OPA1 at the inner mitochondrial membrane (IMM). Mitochondrial fission is driven by the fission machinery complex, which consists of DRP-1, Fis1, and MFF. Mitochondrial hyper-fusion is a pro-survival type, which can increase the ATP production and membrane potential (Δψm), and decrease reactive oxygen species (ROS) and mitophagy [17][26]. (**C**) Proposed model for the nuclear aggregation of mitochondria and the possible interplay among intracellular organelles in response to virus infections. * symbol indicates the possible interaction site. Representative virus that increases the interactions among intracellular organelles is shown with purple rectangle. African swine fever virus, ASFV; Rubella virus, RUBV; Bunyamwera virus, BUNV.

To date, several reports have argued the role of Mfns in innate immunity [27][28][29]. The interaction of Mfns with the adaptor mitochondrial antiviral signaling protein (MAVS) (also called IPS-1, Cardif, or VISA) at the mitochondrial associated membrane (MAM) leads the initiation of the IFN signaling pathway [30][31]. Meanwhile, MAVS was also reported to interact with MFN2, which leads to the inhibition of inflammatory cytokine production, suggesting the MAM plays a complex role in the regulation of innate immunity [28] (detailed in review [31]). Castanier, C et al. also identified the cross-modulation relationship between mitochondrial dynamic and retinoic acid-inducible gene I

protein (RIG-I) like receptor (RLR) signaling activation [27]. Certain viruses, such as influenza A virus (IAV) [32], measles virus (MV) [33], hepatitis B virus (HBV) [34][35][36][37], and hepatitis C virus (HCV) [34], induce selective autophagy to degrade fragmented mitochondria and evade innate immunity. Meanwhile, the non-structural (NS) protein 4B of DENV induces mitochondrial elongation via inactivation of DRP-1 and dampens the activation of RLR signal pathway to promote replication [20]. Similarly, the open reading frame-9b (ORF-9b) encoded by SARS-CoVs causes mitochondrial elongation via triggering DRP-1 degradation, and inhibits RLR signaling [21].

Collectively, viruses have evolved several strategies to hijack the mitochondria for viral genome replication and assembly, including the remodeling of mitochondrial morphology and distribution, the regulation of the fusion–fission machinery complex, and the synthesis of ATP production.

2.1. Rearrangement of ER and unfolded protein response (UPR) during viral infection

The ER, a single continuous membrane, consists of two primary structural subdomains: the nuclear envelope and the peripheral ER (a polygonal network) [38]. The nuclear envelope of ER consists of two flat membrane bilayers; the peripheral ER is composed of membrane cisternae and dynamic interconnected tubules [38][39]. The ER is the largest intracellular endomembrane system and has multiple complex functions, including Ca^{2+} storage, fatty acid synthesis, ion homeostasis, and, in particular, the quality control of newly synthesized proteins [40]. The accumulation of misfolded or unfolded proteins in the ER lumen is known as ER stress [41]. UPR and ER-associated degradation (ERAD) signaling are central to maintain the quality control of the ER [41][42]. The UPR is a signaling cascade aimed at eliminating misfolding proteins and increasing folding capacity in lumen [41]. The protein-folding conditions in the ER lumen is primarily sensed by three integrated signaling transducers: activating transcription factor 6 (ATF6) [43], double-stranded RNA-activated protein kinase-like kinase (PERK), and inositol requiring enzyme 1α (IRE1α) [25][44] (Figure 2). Each branch uses a distinct mechanism to drive the transcription of UPR signal transduction, such as ATF6 by regulated proteolysis, PERK by translational control, and IRE1 by non-conventional mRNA splicing [44]. By contrast, ERAD recognizes misfolded proteins and retro-translocates such proteins into the cytoplasm for degradation by the ubiquitin-proteasome-dependent ERAD and the autophagy-lysosome dependent ERAD [42][45].

A series of studies has reported that viral infections reshape the morphology and membrane remodeling of ER [3][38], and exploit various strategies to hijack the three branches of UPR for viral replication (Figure 2 and Table 1). The possible explanations were summarized as follows: First, the large malleable surface area of ER is used as a physical scaffold to protect viral RNA from degradation by cellular mRNA decay machinery [40][46]. RNA viruses have evolved several strategies to avoid the cellular mRNA decay machinery [46]. Second, viruses, particularly most RNA viruses, remodel the ER membrane to form a variety of structures for infectious progeny [47], including single-membrane spherule vesicles, double-membrane vesicles, convoluted membranes, and single-membrane sheets in the ER lumen [38]. Tenorio, R et al. identified that δNS and μNS of reovirus caused tubulation and fragmentation of the ER, respectively, to re-build replication sites [48], indicating that viral proteins play different roles in the rearrangement of ER membranes. Similarly, the NS4A of DENV induces the membrane arrangement of

ER lumen in a 2K-regulated manner [49]. Third, viruses recruit the ER membranes into the replication and assembly compartments. The viral cytoplasmic replication site of VV [50][51], equine arteritis virus (EAV) [52], and polivirus (PV) [53] is derived directly from the ER membrane. Meanwhile, ASFV structural protein *p*54 plays an important role in the recruitment and transformation of the ER membranes into the envelope precursors [54]. Fourth, viruses increase the capacity and spatial rearrangement to increase ER biogenesis, including membrane protein synthesis, fatty acid change, and Ca^{2+} storage [40]. For enveloped viruses, the key molecular chaperone of ER, including Bip/GRP78 and calnexin/calreticulin, assists the folding of the extracellular domains of viral membrane glycoproteins, such as GP2a of PRRSV [55], and hemagglutinin-neuraminidase (HN) and fusion (F) proteins of NDV [56], when they translocate into the lumen of the ER. Meanwhile, the reprograming of ER biogenesis, such as Ca^{2+} storage, is required for viral replication, including HCV [57] and ASFV [58]. Fifth, viruses co-opt or subvert the ERAD processes to re-establish ER homeostasis, which actively exports the malformed proteins from the ER for degradation. Human cytomegalovirus (HCMV) [59] and IAV [60] exploit the ERAD pathway to benefit viral replication. Finally, the membrane remodeling of ER may suppress the activation of host immunity. Upon viral infections, particularly DNA viruses, stimulator of interferon genes (STING), an activated ER adaptor of the cyclic GMP-AMP synthase (cGAS)-STING signaling pathway, translocates from the ER to the ER-Golgi-intermediate compartment (ERGIC) and the Golgi apparatus, and then activates downstream molecules [61][62][63]. Therefore, we speculate that the morphology remodeling and membrane modification of ER induced by viruses may be involved in the regulation of STING trafficking, EARD degradation, and post-translational modification, and eventually evade the activation of cGAS-STING pathway.

Figure 2. Simplified diagram of the core element of the three unfolded protein response (UPR) signaling branches of the endoplasmic reticulum (ER). During different viral infections, the ER stress activates the three stress sensor proteins: IRE1α, ATF6, and PERK (Detailed in reviews [44][64]). Each sensor uses a distinct mechanism of signal transduction to drive the transcription of UPR target genes and eventually work as feedback loops to mitigate the ER stress [44][64]. Upon ER stresses, ATF6, a transcriptional factor, translocate into the Golgi compartment where it is cleaved by the site (1/2) protease. The N-terminal cytosolic domain of cleaved ATF6 is released into cytosol and then translocated into the nucleus where it binds to ER stress-response elements to activate target genes, including XBP-1 and C/EBP-homologous protein (CHOP) [43]. The activation of PERK inhibits general protein translation by the phosphorylation of eIF2α, enabling dedicated translation of transcripts, including ATF4, a key transducer. The IRE1 branch is regulated by non-conventional mRNA splicing [44][64]. Subsequently, the activated IRE1 processes XBP1 mRNA to generate the spliced form of XBP1 protein (XBP1s), which participates in IRE1α-mediated UPR pathway in response to ER stresses [44][64]. Eventually, the activation of the cleaved ATF6 (N-ATF6), ATF4, and XBP1 transcription factors increases the protein-folding capacity in the ER lumen. Meanwhile, IRE1 and PERK sensors also decrease the load of proteins entering the ER [44][64].

Table 1. Viruses activate and exploit the UPR branch of ER for viral replication.

Viruses	Family	Genome Structure	Virion Structure	Viral Protein	ATF6	PERK	IRE1α	Ref
PRRSV	*Arteriviridae*	Linear, ssRNA(+)	Enveloped; Spherical	?	×	√	√	[55]
IBV	*Coronaviridae*	Linear, ssRNA(+)	Enveloped; Spherical	?	×	×	√	[63]
DENV	*Flaviridae*	Linear, ssRNA(+)	Enveloped; Spherical	?	×	√	√	[65]
JEV	*Flaviridae*	Linear, ssRNA(+)	Enveloped; Spherical	NS4B	√	√	√	[66] [67] [68]
TBEV	*Flaviridae*	Linear, ssRNA(+)	Enveloped; Rounded	?	√	×	√	[69]
HCV	*Flaviridae*	Linear, ssRNA(+)	Enveloped; Spherical	?	√	×	×	[70]
IAV	*Orthomyxoviridae*	Segmented, ssRNA (-)	Enveloped; Rounded	?	×		√	[71]
NDV	*Paramyxoviridae*	Linear, ssRNA(-)	Enveloped; Spherical	F and HN	√	√	√	[56] [72]
MCMV	*Herpesviridae*	Linear, ds DNA	Enveloped; Spherical	?	**?**	√	×	[73] [74]

HSV-1	*Herpesviridae*	Linear, dsDNA	Enveloped; Spherical	UL41/ICP0/ $\gamma_1$34.5	√	√	×	[75] [76] [77] [78]
HBV	*Hepadnaviridae*	Circular dsDNA	Enveloped; Spherical	?	√	×	√	[79]

During different viral infections, the ER stress activates the three stress sensor proteins: IRE1α, ATF6, and PERK (review in the references [44][64]). The following abbreviations are used in this table: murine cytomegalovirus, MCMV; avian coronavirus infectious bronchitis virus, IBV; porcine reproductive and respiratory syndrome virus, PRRSV ; hepatitis C virus, HCV; hepatitis B virus, HBV; influenza A virus, IAV; human herpes simplex virus-1, HSV-1; dengue virus, DENV; tick-borne encephalitis virus, TBEV; Japanese encephalitis virus, JEV; Newcastle disease virus, NDV. The symbols √, ×, and ? indicate activation, inhibition, and unknown, respectively.

2.2. Rearrangement of peroxisome for infectious progeny

The peroxisomes are single membrane-bounded organelles that function in numerous metabolic pathways, including β-oxidation of long-chain fatty acids, detoxification of hydrogen peroxide, and synthesis of ether phospholipids and bile acids [80][81][81, 82]. Notably, the mitochondria and peroxisomes share common functions in the β-oxidation of fatty acids and the reduction of damaging peroxides. Proliferation of peroxisome is largely mediated by growth and division. Peroxisomal division in mammalian cells comprises multiple processes, including membrane deformation, elongation, constriction, and fission [82]. With the exception of peroxin (PEX)11, the peroxisomes and mitochondria share common fission machinery, including DRP-1, Mff, and Fis1 [83][84]. The fission machinery of peroxisome is orchestrated by PEX-11β and mitochondrial fission factors [82]. Mitochondrial-derived vesicles (MDVs) are involved in the transportation of mitochondrial-anchored protein ligase (MAPL), a mitochondrial outer membrane, to peroxisomes [85]. The retromer complex containing vacuolar protein sorting (Vps) 5, Vps 26, and Vps 29, a known component of vesicle transport from the endosome to the Golgi apparatus, also regulates the transport of MAPL as a binding partner from the mitochondria to peroxisomes [86].

Viruses regulate the morphology and biogenesis of peroxisomes to promote progeny replication [1]. For instance, the C-terminal of the rotavirus VP4 protein is directly located in peroxisomes via its conserved peroxisomal targeting signal [87]. Meanwhile, viruses have exploited the myristoyl-CoA produced by peroxisome biogenesis for the N-myristoylation of viral proteins [1], such as ASFV [88], indicating that peroxisomal lipid metabolism contributes to viral replication. Another typical example is the tomato bushy stunt virus (TBSV), a member of the *Tombusviridae* family, which infects a variety of plant species. McCartney, A.W et al. reported that TBSV induced the rearrangement of peroxisomes and caused vesiculation of the peroxisomal membrane, where it provided a scaffold for virus anchoring and server as the sites of viral RNA synthesis [89]. In the absence of peroxisomes, TBSV also

exploits the surface of the ER membrane as a viral factory for viral replication and assembly [90]. It is suggestive of the remarkable flexibility of the virus to use host membranes for replication.

2.3. Hijacking of Golgi apparatus for infectious progeny

The Golgi apparatus is a highly dynamic organelle whose function primarily includes saccule formation and utilization of such saccules in vesicle formation at the opposite face for delivery [91]. The normal cellular secretory pathway, bidirectional transport between the ER and Golgi apparatus, is mediated by tubulovesicular transport containers that depend on two coat protein complexes, COP-I and COP-II. The COP-II establishes a membrane flow from the ER to the Golgi complex [92]. However, the COP-I coat acts in retrograde transport from the Golgi back to the ER [93].

In general, certain viruses utilize the cellular trafficking and secretory pathway of the ER-Golgi transport system to replicate/release their progeny [3]. PV utilizes the components of the ADP-ribosylation factor (Arf) family of small GTPases [94] and cellular COP-II proteins [95] to form membrane-bound replication complex for viral replication, indicating that PV hijacks the components of the cellular secretory pathway for replication. As shown in Table 2, metonaviridae [23] and peribunyaviridae [24] hijack the Golgi complex to re-construct it as a viral factory for viral replication. For example, RUBV [23] and BUNV [24] infections modify cell structural morphology and remodel the Golgi complex as a viral factory during the entire life cycle. Furthermore, host secretory signaling is also crucial for innate and acquired immune responses, such as the exportation of proinflammatory and antiviral cytokines. Nearly 25 years ago, Doedens, J.R et al. reported that the 2B and 3A proteins of PV inhibited cellular protein secretion by directly blocking the transportation from the ER to the Golgi apparatus [96], indicating that the functional secretory protein is not indispensable for viral RNA replication. Mechanistically, Dodd, D.A et al. identified that the inhibition of 3A protein of PV on the ER to Golgi limited the antiviral cytokine secretion of native immune response and inflammation, including interleukin-6, interleukin-8, and β-interferon [97]. Deitz, S.B et al. also identified that PV 3A protein reduced the presentation of new antigens on the cell surface [98]. Considering that the ER adaptor STING was also located on the Golgi and ERGIC [60], we hypothesized that the membrane remodeling and modification of Golgi induced by viruses might also be involved in the regulation of cGAS-STING pathways (Figure 3). Collectively, all these data suggest that enteroviruses, such as PV and CVB, have evolved a series of strategies to hijack cellular trafficking and secretion for viral replication.

Table 2. Intracellular compartment sites for viral replication and assembly.

Family	Viruses	Genome Structure	Virion Structure	Replication Site	Ref	Assembly Site	Ref
Asfarviridae	ASFV	Liner, dsDNA	Enveloped, spherical	Nuclear and cytoplasmic	[16] [99] [100]	ER	[54] [58]

Poxviridae	VV	Liner, dsDNA	Enveloped, brick-shaped	cytoplasmic	[101]	ERGIC, ER	[50] [51]
Arteriviridae/Ariteriviruses	EAV, PRRSV	Liner, ssRNA (+)	Enveloped, spherical	Cytoplasmic double membranes	[51] [102]	ER	[52]
Coronaviridae/Coronavirus	SARS/MHV	Liner, ssRNA (+)	Enveloped, spherical	Cytoplasmic double membranes	[103]	ERGIC, Golgi, ER	[104] [105]
Flaviviridae/ Hepacivirus	HCV	Linear, ssRNA(+)	Enveloped, spherical	Cytoplasmic	[106]	Autophagosome	[107] [108]
Metonaviridae/Rubivirus	RUBV	Liner, ssRNA (+)	Enveloped, spherical isometric capsid?	Cytoplasmic	[23]	Golgi, Lysosome	[23] [109]
Nodaviridae	FHV	Linear, ssRNA(+)	Non-envelop, icosahedral	Cytoplasmic	[110] [111]	OMM	[110] [111]
Togaviridae/Alphavirus	SFV	Liner, ssRNA (+)	Enveloped, spherical and icosahedral	Cytoplasmic	[112] [113]	Endosome /Lysosome	[112] [113] [114]
Tombusviridae	TBSV	Linear, ssRNA(+)	Non-envelop, icosahedral	Cytoplasmic	[90]	Peroxisome, ER	[89] [90]

Picornaviridae/Enterovirus	CV/PV	Linear, ssRNA(+)	Non-envelop, spherical	Cytoplasmic	[115]	ER	[52] [115]
Orthomyxoviridae	IAV	Segmented, ssRNA (-)	Enveloped; Rounded	Nuclear	[116]	ER, Golgi	[116]
Peribunyaviridae/Bunyavirus	*BUNV*	Segmented, ssRNA (-)	Enveloped, spherical	cytoplasmic	[24]	Golgi	[24] [117]
Retroviridae/Lentivirus	HIV	Linear, ssRNA(+)	Enveloped, Spherical	Nuclear	[118]	ER or Golgi	[118]

The following abbreviations are used in this table: African swine fever virus, ASFV; rubella virus, RUBV; Bunyamwera virus, BUNV; semliki forest virus, SFV; Flock house virus, FHV; tomato bushy stunt virus, TBSV; severe acute respiratory syndrome, SARS; murine hepatitis virus, MHV; porcine reproductive and respiratory syndrome virus, PRRSV ; equine arteritis virus, EAV; influenza A virus, IAV; human immune deficiency, HIV; vaccinia virus, VV; poliovirus, PV; coxsackieviruses, CV. reticulum-Golgi intermediate compartment, ERGIC; outer mitochondrial membranes, OMM.

2.4. Role of the lysosome and endosome in viral infections

The lysosome, an acidic and membrane-bound organelle, acts as a cellular recycling center and is filled with a number of hydrolases [119]. The lysosome-based degradation processes are subject to reciprocal regulation [120]. Lysosomes degrade unwanted materials which are delivered either from outside via the endocytic pathway or from inside via the autophagic pathway [120][121]. For viral replication and assembly, certain viruses, including *Alphaviruses* [113], such as semliki forest virus (SFV) [112], exploit the membrane surface of the endosome and lysosome as a viral factory. Similarly, RUBV also can modify the membrane of lysosomes for a viral factory [109]. Meanwhile, the Toll-like receptors (TLR), such as TLR 3/7/9, are located on the endosome, indicating that the endosome also plays an important role in innate immunity [61]. Therefore, we speculate that another possible strategy is that viruses, particularly DNA viruses, evade the TLR-mediated activation of the NF-κB and transcription of proinflammatory cytokines. HBV infection suppresses TLR-9 expression and prevents TLR9 promoter activity in human primary B cells [122]. Interestingly, DENV, a positive-stand RNA virus, activates the TLR9 by inducing mtDNA release in human dendritic cells [123]. Additionally, the endosomal-lysosomal sorting system is a complex and dynamic vesicular sorting signaling, which is fundamental to maintain homeostasis [124]. Viruses, particularly

enveloped viruses such as HIV [118], have evolved several strategies to hijack the endosomal sorting complex required for the transport (ESCRT) complex to facilitate viral budding. Collectively, all these data indicate that different viruses utilize different strategies to hijack the endosome/lysosome for viral progeny.

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