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Review

Organelle dynamics and viral infections: at cross roads

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Abbreviations:
VACV
Vaccinia Virus
DENV
Dengue Virus
SARS-CoV
Severe Acute Respiratory Syndrome Corona Virus
UPR
Unfolded Protein Response
ERAD
Endoplasmic Reticulum Associated Degradation
SV40
Simian Virus
HIV
Human Immunodeficiency virus
HSV
Herpes Simplex Virus
Ad
Adeno Virus
HBV
Hepatitis B Virus
PML NB
Promyelocytic Leukemia Nuclear Bodies
HFFs
Human Foreskin Fibroblasts
HCMV
Human Cytomegalovirus

ABSTRACT

Viruses are obligate intracellular parasites of the host cells. A commonly accepted view is the requirement of internal membranous structures for various aspects of viral life cycle. Organelles enable favourable intracellular environment for several viruses. However, studies reporting organelle dynamics upon viral infections are scant. In this review, we aim to summarize and highlight modulations caused to various organelles upon viral infection or expression of its proteins.

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Huh
Human Hepatoma cell lines
HCV, Hepatitis C Virus
ROS
Reactive Oxygen Species
MPTP
Mitochondria Permeability Transition Pore
MMP
Mitochondrial Membrane Potential
CMV
Cucumber Mosaic Virus
SFV
Semliki Forest Virus
ESCRT
Endosomal Sorting Complexes Required for Transport
PV
Polio Virus

A unique feature of eukaryotic cells is the presence of distinct membrane bound structures called organelles. This sub-compartmentalization of eukaryotic cells is very essential for its optimum function. Organelles achieve this due to the presence of a unique set of proteins and distinctive lipid composition that determines their function. They are dynamic and interact with the surrounding organelles to regulate their biogenesis and function [1,2]. Association of organelle dysfunction with human diseases/disorders is reported and widely acknowledged [3]. It is interesting that not only organelles are required for proper functioning of cells, but are also required for the successful infection of a virus [4,5]. It is well established that viruses develop alternate strategies to survive in the cells. The steps of the viral life cycle include entry, translation, replication, assembly and egress [6]. Moreover, viruses have developed remarkable ways to complete their life cycle by targeting specific cell organelles and processes. Organelles like mitochondria, ER, peroxisomes play an important role in innate immunity and host defence [7]. Recently lipid droplets have also been reported to be essential for innate response against viral infection [8].

The viral life cycle is also a dynamic process that leads to the extensive host cellular reorganization. Characterization of this spatiotemporal reorganization is a key step in order to understand the molecular mechanism of viral infection. Localization of the viral proteins to an appropriate sub-cellular compartment is part of the strategy to hijack the host machinery and necessary pathways leading to establishment of an infection [9,10]. With the advent of several modern microscopy and proteomics methods, it is now clear that the localization and function of many host proteins are altered due to viral infections. Not only the host proteins but the intracellular localization of the viral proteins and their interactions with the host proteins are also extensively studied using these methods [10]. However, currently our understanding of organelle dynamics during viral infections is still at its infancy. Current review briefly summarizes our knowledge of the various cell organelles/compartments following virus infection. This topic at the interjection of virology and cell biology represents an emerging research area of molecular investigations in virology.

1. Nucleus

Presence of nucleus that houses the genome is what distinguishes eukaryotic cells from prokaryotes (Fig. 1). It is a double membrane organelle and is the site for gene regulation and transcription. Nuclear envelope comprising of nuclear pores is the barrier between the nuclear content and the rest of the cell. Nucleolus is the region where ribosomal subunit assembly takes place in the nucleus. Sub nuclear structures comprising of several proteins which regulate many cellular processes like apoptosis, DNA damage, *etc* are called PML-NBs.

1.1. Alterations aiding nuclear entry of viruses

Many DNA and RNA viruses depend on the host nuclear proteins for their replication [11]. Several strategies are used by viruses in order to deliver its genome to the host cells [12]. Usually, when cells undergo mitosis, there is a temporary disassembly of the nuclear envelope (NE) which allows some viruses to enter into the nucleus [13]. Entry and integration of murine leukemia virus (MLV) into host nucleus depends on the NE breakdown during mitosis [14]. Various human immunodeficiency virus (HIV) pre-integration complex proteins, such as the matrix [15], Vpr [16], integrase [17,18] were found to contain nuclear localization signal (NLS) in their genome sequence. This NLS interacts with the nuclear transport receptors, which transports the viral proteins through the nuclear pore complex (NPC). Similarly, the influenza virus nucleoprotein (NP) present in the viral ribonucleoprotein complex (vRNP) contains NLS1, NLS2 and NLS3, which helps in its binding to cellular importins resulting in transportation of the vRNP to the nucleus [19–21].

In another strategy, the capsid of certain viruses gets attached to the cytoplasmic side of the host NPC either directly or with the help of importins. This interaction acts as a signal for capsid disassembly followed by entry of the viral genome along with their proteins through the NPC into the nucleus [12]. Studies on the herpes simplex virus-1 (HSV-1) infection on Vero, BHK-21 and PtK_2 cells reported transportation of viral tegument-capsid by dynein to the cytoplasmic side of NPC [22,23]. The HSV-1 capsid binds to NPC with the help of importin β and subsequently releases DNA into the nucleus through the NPC [24]. Similarly, the capsid protein of adenovirus (Ad) on binding with the nuclear transport protein Nup214 attaches to the cytoplasmic side of NPC and releases the genetic material into the nucleus [25]. Some small viruses such as hepatitis B virus (HBV), baculovirus, *etc* were found to cross the NPC and release their genome at the nuclear side of NPC or within the nucleus [12]. The capsid protein of HBV was reported to interact with NPC via the nuclear receptor Nup153 in *Xenopus laevis* oocytes [26]. Furthermore, this binding depends on importin α, β and phosphorylated core protein present on its capsid [27]. Upon infection, HBV capsid enters the nucleus through the NPC and subsequently releases its genome into the nucleoplasm [28].

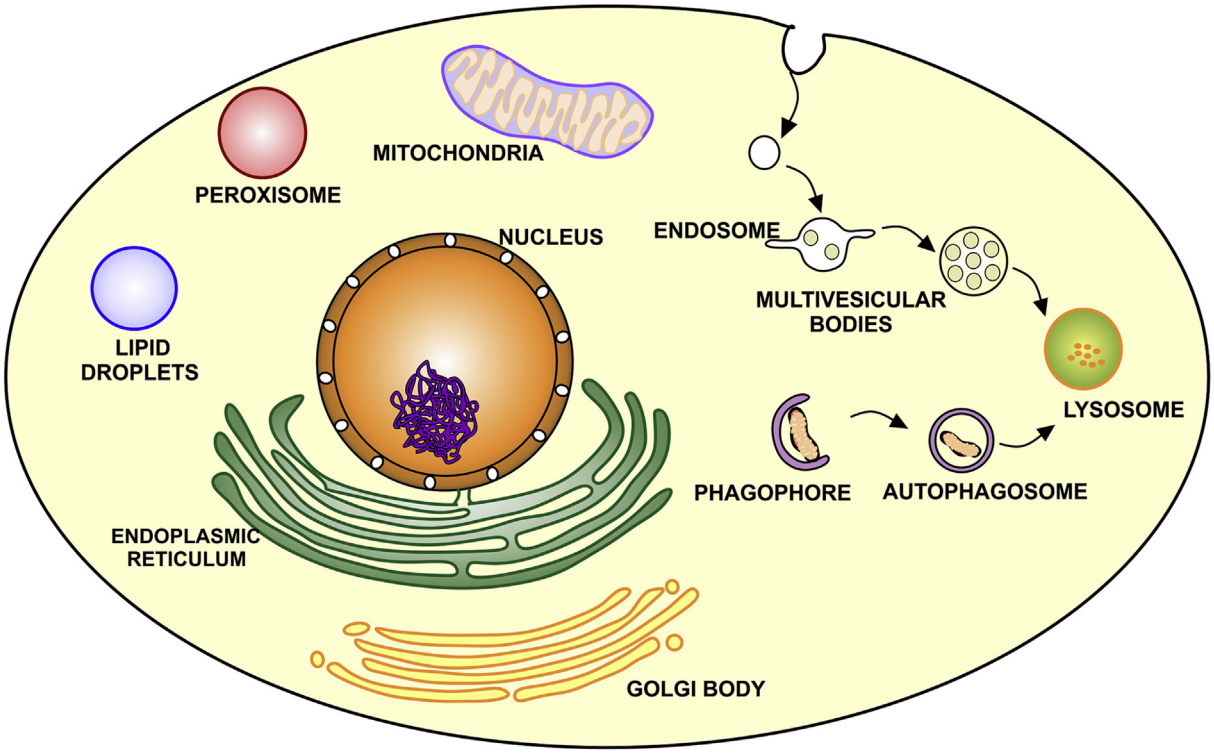

Fig. 1. A representative eukaryotic cell (animal cell) depicting various organelles. Organelles such as the nucleus, ER, Golgi; Mitochondria, Peroxisome, Lipid droplet, Lysosome, and other vesicular compartments like endosomes, multivesicular bodies, autophagosomes are essential for optimum functioning of a cell. A unique protein and lipid composition apart from their function is what defines each of them. A dynamic view of the cells where several organelles interact with their surrounding organelles spatio-temporally is widely accepted now.

Similarly, capsid proteins of simian virus 40 (SV40) were found to enter the nucleus through NPC [29]. It has been reported that the disruption of the NE and nuclear lamina temporarily aid the nuclear entry of viruses such as parvoviruses [30]. Disruption of NE in *Xenopus* oocytes and both NE and nuclear lamina in mouse fibroblast cells upon parvovirus infection and minute virus of mice (MVM) was reported using electron microscopy analysis [30,31]. Presumably, viruses evolved different mechanisms to enter nucleus in order to facilitate their replication cycle and survivability inside the host cells.

1.2. *Effect on nucleolus*

After the successful entry into the nucleus, both DNA and RNA viruses exploit various nuclear components such as nucleolus, promyelocytic leukaemia nuclear body (PLN) and/or nuclear proteins in order to facilitate their replication (Fig. 2) [11]. Nucleolin, fibrillarin and B23 (nucleophosmin) are examples of nucleolar proteins reported essential for various functions like post transcriptional process, ribosome assembly, *etc* [32]. These multifunctional host nucleolar proteins were reported to be incorporated into the replication and translation complex of many viruses [11]. Many DNA viruses like HSV and Ad were reported to be involved in relocalization or disruption of the host nucleolar proteins [11]. For instance, the transfection of the recombinant UL24 protein of HSV-1, tagged with an N-terminal hemagglutinin in Vero cells resulted in the redistribution of nucleolin and B23 [33,34]. Another nucleolar protein fibrillarin was also found to be redistributed in spots throughout the nucleus but in an UL24 independent manner [33]. The core protein of Ad was found to be associated with the nucleolus in HeLa cells [35]. Further studies showed that this association results in the relocation of the nucleolin to the cytoplasm of the infected cells [36]. The Ad-induced relocation of nucleolin was proposed to be a strategy used by virus to suppress its activity [36]. Additionally, infection of HeLa cells with Ad resulted in inhibition of synthesis and maturation of rRNA [37].

Nucleolar localization of the viral capsid and RNA binding proteins of many RNA viruses has been reported [11]. For example, the encephalomyocarditis viral (EMCV) proteins 2A and 3BCD and human rhinovirus HRV 3C protease were found to localize to the nucleoli resulting in inhibition of cellular RNA transcription [38,39]. It has been reported that the expression of Tat and Rev proteins of HIV-1 in COS7 cells resulted in their accumulation in dense fibrillar component in the nucleolus [40]. Moreover, Rev protein was reported to be involved in deforming the nucleolar architecture [40]. Similarly, the viral N protein was found to be localized to the nucleolus in addition to the cytoplasm upon infection of coronavirus resulting in delayed cell cycle to facilitate viral assembly [41]. Poliovirus (PV) or rhinoviruses interact with nucleolin and blocks the nuclear import leading to accumulation of nucleolin in the cytoplasm of the infected cells [42]. The accumulated nucleolin interacts with the internal ribosome entry site (IRES) element present in the upstream 5′ end of the viral genome to stimulate its translation [43]. On the other hand, these changes result in the shutdown of cellular transcription leading to the downregulation of the host defence mechanism [42]. Infection of human respiratory syncytial virus (HRSV) in A549 cells resulted in depletion of nucleolin [44]. Although, both DNA and RNA viruses behave differently towards acquiring the nuclear niche however the goal being to establish control over cellular transcription and favour its genome over the host.

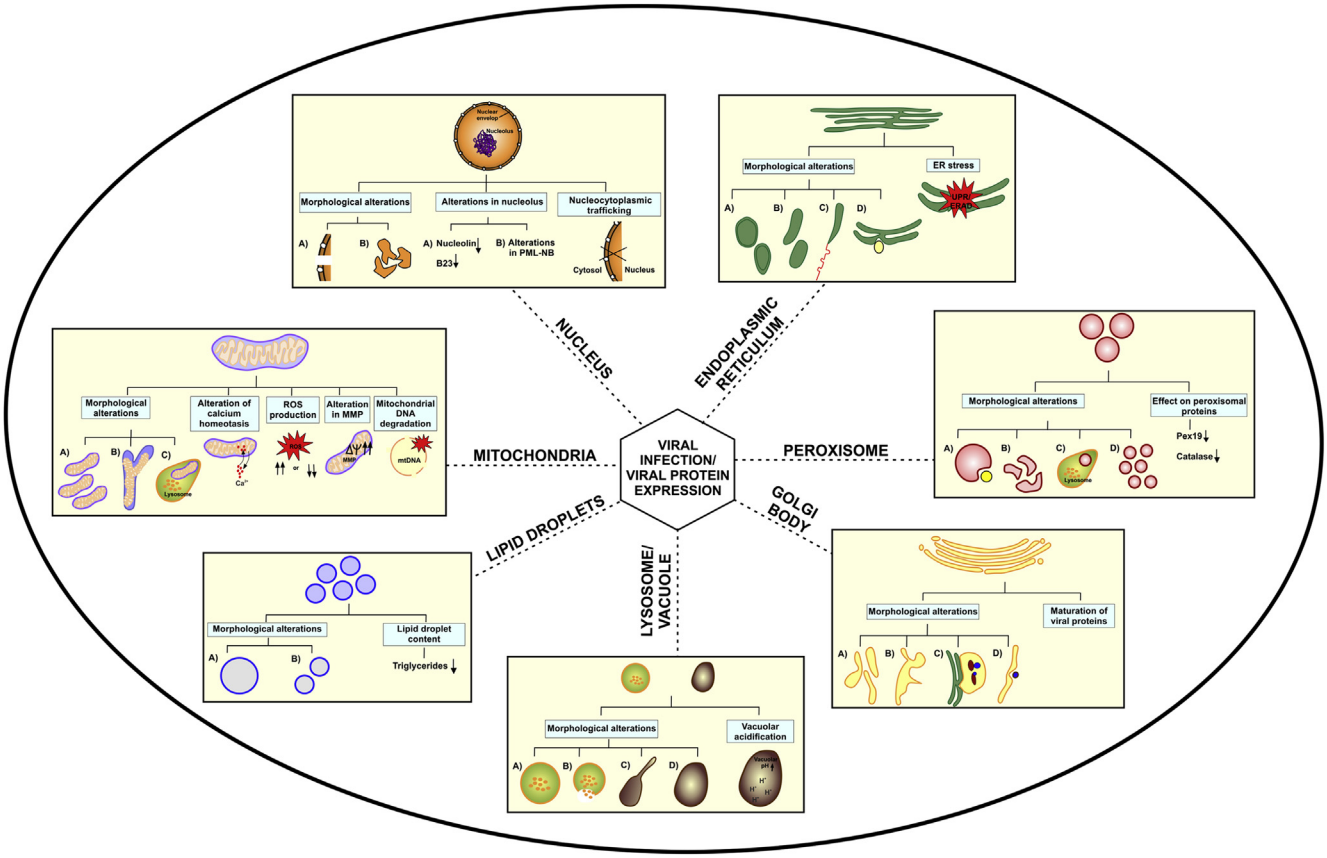

Fig. 2. Alterations caused to various cellular organelles upon viral infection or viral protein expression in a host cell. The figure represents an overview of various cell organelles and the alterations in them as a result of viral infection or viral protein expression as described in the manuscript. Disruption of the nuclear membrane and fragmentation of the nucleus are the two most common morphological alterations of the nucleus observed. Many viruses are also involved in relocalization or depletion of host nucleolar proteins like nucleolin, B23 *etc* and alterations in the sub-nucleolar PML-NB is also reported. Another major alteration caused due to viral infections is disruption of the nucleocytoplasmic trafficking in the host cell. Several morphological alterations such as formation of single membrane tubules and double membrane vesicles (DMVs), vesicle formation, zippered appearance, *etc* of the ER are reported upon viral infection. Viruses also interfere with the host post translational machinery resulting in ER stress like UPR and ERAD. Peroxisomes are another set of organelles which have been reported to be a favourable site for the virus in a host cell: Modifications like vesicular structures called "profoundly modified peroxisomes" or "peroxisome derived multivesicular bodies" are reported in some cell types. Other morphological alterations include fragmentation, degradation and increase in the number of peroxisomes. Reduced levels of peroxisomal membrane protein Pex19 and matrix protein catalase have also been reported in such cells. Various morphological alterations of golgi bodies like disruption and fragmentation, deformation of the membranes into pseudo-circular and pleomorphic structures, amalgamation of golgi apparatus and ER, vesicle formation, *etc* have been reported as a result of viral infections. Several viral proteins also localize to the golgi body and mature by undergoing post translational modifications. Swelling up and induction of lysosomal rupture is a common alteration caused due to viral protein expression in cells. Formation of a large intracellular vacuole, tubulation of vacuolar membrane and vacuolar acidification as a result of virus infections are reported. Reduced number of lipid droplets and enhanced size of the organelles was reported. Another important alteration in lipid droplets is the decreased level of triglycerides. Viral infection induces morphological alterations of mitochondria like enhanced fission, fusion and mitophagy. Loss of calcium homeostasis in a cell, ROS imbalance, effect on MMP and degradation of mitochondrial DNA are other alterations leading to mitochondrial dysfunction.

1.3. Effect on promyelocytic leukemia nuclear bodies (PML NB)

PML NB is another subnucleolar component, which contains proteins such as PML and Sp100. These proteins are induced by interferons and hence PML NB can act as a target for viruses to escape the antiviral signalling response [45]. Redistribution of the PML NB has been reported upon infection of HSV-1 to BHK-21 cells [46]. Similarly, EBNA LP protein of Epstein-Barr virus (EBV) was found to displace Sp100 from PML NBs in Burkitt's lymphoma and Hep2 cells [47]. The viral E4-ORF3 protein induced reorganization of PML NBs into elongated track like structures upon infection of CV1 cells with human Ad5 [48]. Later, it was found that this reorganization was responsible for the downregulation of the host antiviral response [49]. Another example is the infection of human foreskin fibroblasts (HFFs) with human cytomegalovirus (HCMV) resulting in the accumulation of pp71 at PML NBs in the infected cells [50]. Further studies showed that pp71 was responsible for the proteasomal degradation of PML-NB protein Daxx, which is important for inducing intrinsic immune response against HCMV infection [50]. Some RNA viruses also result in the redistribution and degradation of host PML NBs in order to neutralize the antiviral response. The RING finger protein Z of lymphocytic choriomeningitis virus interacts with PML protein and leads to the redistribution of PML-NBs from the nucleolus to the cytoplasm [51]. The expression of 3C protease of EMCV in CHO cells was reported to target PML-NBs and promote its degradation in proteasome and by SUMO-dependent mechanism [52]. Interestingly, CHO cells infected with rabies virus were reported to contain enlarged PML NBs [53].

1.4. Other alterations

Disruption of the nucleocytoplasmic trafficking in the host cells is another major alteration caused due to viral infections (Fig. 2) [54]. Two conserved proteins pUL50 and pUL53 of HCMV were reported to remodel the nuclear lamina of HELFs (primary human

lung fibroblasts) for the budding of virions [55]. Interaction between human papillomavirus (HPV) and host mitotic chromosomes has been documented [56]. Infection of porcine bone marrow cells with African swine fever virus (AFSV) resulted in fragmentation of the nucleus [57].

2. Endoplasmic reticulum (ER)

The organelle found in continuation with the nucleus in a cell is the ER (Fig. 1). Protein synthesis and folding (rough ER), lipid synthesis, calcium regulation (smooth ER), *etc* are some of the important functions of the ER. Multiple structural domains of the ER are reported which enable it to serve as a site for various important functions in a cell.

2.1. Effect on ER morphology

Several morphological alterations of ER such as vesicle formation, invagination of the membrane, zippered appearance, *etc* have been reported upon viral infection in different cell lines (Fig. 2). The large malleable surface of the ER aids viruses to form protective compartments to set up their replication machinery. These compartments known as viroplasm not only concentrate viral and host proteins required for viral genome replication but also protect the viral genome from cellular nucleases [58]. In order to construct these compartments, viruses alter host's fatty acid metabolism, induce rearrangement of the membrane constituents and also recruit cellular machinery to produce proteins essential for its replication [59,60]. Infection of vaccinia virus (VACV) in BS-C-1, HeLa and RK-13 cells leads to the formation of VACV membranes derived from the ER membrane [61]. In case of dengue virus (DENV-2), the genomic RNA was observed to localize over the rough ER in C6/36 *Aedes albopictus* cells [62]. DENV infection in Human hepatoma 7 (Huh7) cells leads to invagination of ER membrane resulting in the formation of spherules or vesicles containing double stranded RNA [63]. HeLa cells and COS-1 cells on infection with PV 1 cause formation of single membrane tubules which later mature into double membrane vesicles (DMVs) [64,65]. Similarly, severe acute respiratory syndrome corona virus (SARS-CoV) induced formation of ER derived DMVs upon infection of Vero cells [66,67]. Zippered appearance of ER was observed upon infection of infectious bronchitis virus (IBV) on mammalian, avian and tracheal epithelial cells [68]. Studies with the plant viruses like the potato virus X (PVX) reported TGBp2 protein induced reorganization of the ER and appearance of vesicular structures in tobacco plants [69]. Effect of the viral protein expression on sterol biosynthesis apart from the alterations in ER morphology have also been reported [59,70].

2.2. ER stress

Several viral proteins need to be glycosylated at their N-terminal to ensure proper folding and for the incorporation into virions [71]. Hence, a common phenomenon observed upon viral infection is interference with the host post translational machinery and competition with the cellular proteins to undergo these modifications [72]. For example, protein pORF2 of hepatitis E virus (HEV) gets glycosylated in the ER upon its expression in COS-1 cells and Huh7 mammalian cells [73,74]. This increased biosynthetic load is proposed to increase in accumulation of malformed proteins resulting in ER stress (Fig. 2). ER gets relieved from this stress by inducing a pathway called unfolded protein response (UPR) pathway [72]. UPR serves to enhance the cell's degradation ability in order to establish ER homeostasis [72]. Transport of misfolded, misassembled proteins from the ER to the cytosol and clearance by the ubiquitin proteasome system takes place via the ER associated degradation (ERAD) pathway [72]. However, some viruses use ERAD pathway for their advantage by co-opting ERAD to disassemble and gain access to the cytosol of the host cell [75]. Upon SV40 infection of CV-1, HeLa and 3T6 cells, induction of ERAD factors in turn induce ER membrane reorganization into distinct subdomains called foci and the accumulation of SV40 in these foci was observed [76]. Later, SV40 particles travel across the ER membrane to reach the cytosol [76]. Many enveloped and non-enveloped viruses that exploit ER functions like UPR, ERAD to facilitate their replication have been discussed elsewhere [71].

In addition to the above listed mechanisms, ER mediated N-linked glycosylation plays a very important role in the survival of the viruses. It has been very elegantly demonstrated that the biogenesis of influenza could modulate the host immune response [77]. Similarly, the role of N-glycans in the host immunity against HIV has been documented [77]. These studies corroborate to a common point where the level of glycosylation in the viral surface glycoproteins could alter their antigenicity.

3. Mitochondria

Mitochondria are double membrane bound organelles that comprise their own genome (Fig. 1). They are involved in various functions like fatty acid metabolism, apoptosis, calcium homeostasis, *etc*. Considered evolutionarily the oldest organelle of a eukaryotic cell, they are indispensable as power house of the cell.

3.1. Effect on mitochondrial morphology and intracellular distribution

Mitochondrial morphology is maintained by a series of interlinked events namely mitochondrial fusion, fission and mitophagy [78]. Mitochondrial fusion helps in exchanging matrix metabolites and intact mitochondrial DNA while mitochondrial fission helps in sorting impaired mitochondria from the healthy population which are further eliminated by a process called mitophagy [79]. All the above dynamic events are altered upon viral infection in order to facilitate its replication (Fig. 2) [80]. For example, it was reported that HBV infection in the cell induces mitochondrial fission followed by mitophagy in order to attenuate apoptosis [81]. On the other hand, expression of ORF-9B protein of SARS-CoV virus promoted mitochondrial fusion in HEK293 cells [82].

Upregulation of mitophagy and degradation of the mitochondrial antiviral signalling protein (MAVS) in order to attenuate the antiviral immune response in non-small cell lung cancer (NSCLC) cells was reported upon measles virus infection [83]. The expression of matrix protein (M) of human parainfluenza virus type 3 (HPIV3) in HEK293T and HeLa cells was reported to induce mitophagy resulting in the suppression of type1 interferon response [84]. HBV induces mitophagosome formation which upon fusion with lysosomes leads to mitophagy and prevents apoptosis, thus facilitating persistent infection in the Huh7 cells [81]. Similarly, Newcastle disease virus (NDV) was reported to induce mitophagy, which promotes NDV replication by preventing caspase dependent apoptosis in human non-small cell lung cancer A549 cells [85]. Viruses can alter the intracellular distribution of mitochondria either to prevent the release of mediators of apoptosis or to meet their energy requirement during replication by concentrating them near their viral factories [86]. HBV X protein induces the perinuclear clustering of mitochondria in Huh7 cells [87] and AFSV leads to the transport of mitochondria to viral assembly sites in Vero cells [88].

3.2. Effect on mitochondrial DNA

Mitochondrial DNA codes for proteins essential for respiratory functions of a cell. Certain viruses evade the mitochondria associated antiviral response by damaging the host cell mitochondrial DNA, which is essential for synthesizing enzymes for optimum mitochondrial function [86]. For example, mitochondrial DNA degradation is induced in mammalian cells upon expression of UL12.5, an amino-terminally truncated UL12 isoform of HSV-1 [89]. Raji cell lines infected with hepatitis C virus (HCV) also exhibit mitochondrial DNA depletion [90].

3.3. Effect on calcium homeostasis

Maintenance of mitochondrial/cellular Ca^{2+} homeostasis is vital for various cellular functions. Many viruses are involved in altering the mitochondrial calcium homeostasis in order to meet their needs during replication [86]. HCMV upon infection causes calcium influx into mitochondria from ER [91]. On the other hand, expression of 2B protein of coxsackievirus resulted in reduced signalling of Ca^{2+} between the ER-Golgi and the mitochondria in HeLa cells resulting in suppression of apoptosis [92]. Rotavirus was also reported to alter the calcium homeostasis in the host cell throughout its life cycle [93].

3.4. Reactive oxygen species (ROS) production

Mitochondria are the major source of ROS in a cell and a balance between ROS production and scavenging is crucial for optimum functioning of the cells. Upon viral infection mitochondria undergo oxidative stress and result in an increased production of ROS which in turn reduces virus replication [86]. Interestingly, ROS is also involved in activating many host cellular pathways favourable for viral replication and pathogenesis. Several viruses like HIV, HCV, AdV, EBV, *etc* result in increased oxidative stress upon infection [86]. On the other hand, both increase and decrease of oxidative stress is employed as a survival strategy by HBV [94,95].

3.5. Effect on mitochondrial membrane potential (MMP)

Many viral proteins reach mitochondria through the mitochondria-associated membrane [96] a sub-compartment of the ER or are targeted directly from the cytosol and result in an altered mitochondrial permeability transition pore (MPTP) [97]. MPTP is also responsible for the maintenance of MMP and provides energy for ATP synthesis. Altering MPTP leads to passive swelling, outer membrane rupture, osmotic water flux, and release of pro-apoptotic factors leading to cell death [98]. In general, increased MMP induces apoptosis, while decreased MMP prevents apoptosis [86]. Viruses are proposed to decrease MMP to prevent cell death in order to promote their replication. However, in later stages, they may trigger an increase in MMP to release the progeny virions by apoptosis [86]. The M11L protein of myxoma pox virus prevents the loss of MMP in Cos-7 monkey kidney cells, HeLa cells, THP-1 human monocytes and Jurkat T lymphocytes [99]. On the other side, the R protein of HIV-1 induces the loss of MMP in CEM-C7 and Jurkat cells and results in apoptosis [100].

3.6. Effect on mitochondrial metabolic pathways

Viruses alter the host mitochondrial metabolic pathways in order to maintain cellular energy homeostasis essential to ensure efficient replication and to avoid mitochondrial antiviral response particularly in case of slow replicating virus [101]. Some viruses modulate the normal cells to increase aerobic glycolysis and use glucose biosynthetically, which helps especially enveloped viruses to increase their available pool of fatty acids, lipids and nucleotides during their replication [102,103] The feline leukemia virus infection on lung fibroblasts (FLF-3) resulted in a 30–40% increase in glucose uptake and lactic acid production [104]. An increase in the lactic acid production upon infection of the chick embryo cells with Rous sarcoma virus was reported [105]. HCMV upon infection of HFFs, human retinal pigment epithelial cells (ARPE19), human embryonic lung fibroblasts (MRC5) and Vero cells enhances glycolytic flux and directs the supply of carbon from glucose to TCA cycle. This helps to facilitate fatty acid biosynthesis while HSV-1 upon infection of same cell lines directs the central carbon metabolism in order to induce the production of pyrimidine nucleotide components [106]. HCV core protein suppresses mitochondrial complex 1 activity and impaired function of electron transport cycle leading to ROS accumulation in hepatoma cells of transgenic mice [107].

Mitochondrial involvement in virus survival is quite relevant to the fact that viruses require a source of energy to favour the active processes involved in their life cycle.

4. Peroxisomes

Peroxisomes are single membrane bound dynamic organelles required for β-oxidation of fatty acids and ROS metabolism (Fig. 1). They have developed diverse functions which are organism and environment dependent. They are unique with respect to proliferation, as they can increase in number by both growth and division of pre-existing organelles and formation of new organelles from the ER.

4.1. Localization of viral proteins to peroxisomes

Many viruses or viral proteins are reported to localize to peroxisomes and/or exploit their functions to facilitate their replication in the host cells [108]. Presence of a peroxisome targeting signal (PTS) in the protein sequence is reported to be essential for targeting proteins into the peroxisomes [109]. However, it was also proposed that viral proteins without PTS may get associated with host peroxisomal proteins in the cytosol which then ferry the viral protein into the peroxisomes in a piggyback fashion [108]. For instance, HCMV encodes a protein called vMIA reported to be localized to peroxisomes in HFFs and HepG2 cells [110]. The vMIA interaction with the host Pex19 protein aids the viral protein localization to the peroxisomes. Fragmentation of peroxisomes upon vMIA expression in HepG2 was also reported [110]. In addition, peroxisomal localization of two cymbidium ring spot viral proteins p33 and p92 was reported in yeast [111]. A role for peroxisomes in the replication of TBSV has also been reported. The viral replication protein p33 interacts with the host peroxisomal protein Pex19 for its targeting to the peroxisomal membrane and subsequent replication [112,113]. The host hsp70 protein was reported to promote the localization of the viral replication proteins to the peroxisomes in yeast cells [114]. N-terminal protease N^{pro} of pestivirus is another example of a viral protein that is associated with peroxisomes and facilitates its survival and replication [115].

4.2. Effect on peroxisome morphology/biogenesis

Some members of the family *tombusviridae* are involved in remodelling the peroxisomal membrane resulting in the formation of vesicular structures called “profoundly modified peroxisomes” or “peroxisome derived multivesicular bodies” [108]. For example, the infection of cymbidium ring spot virus resulted in the formation of small vesicles at the periphery of the peroxisomes in plant leaf

tissues [116]. At the later stage of infection, the entire peroxisomal matrix is occupied by these vesicles [116]. Similarly, the cucumber necrosis virus (CNV) induces the formation of peroxisomal vesicles in which the viral RNA replication occurs in yeast cells [117]. Studies revealed upregulation of peroxisomal biogenesis in endothelial cells upon latent infection of Kaposi's sarcoma associated herpes virus [118]. It was also reported that proteins involved in peroxisomal lipid metabolism were essential for the survival of latently infected human dermal microvascular endothelial cells and lymphatic endothelial cells [118]. Interestingly, HIV infection reduces the number of peroxisomes in infected cells due to upregulation in the levels of microRNAs that inhibit production of peroxisome biogenesis factors [119].

4.3. Effect on peroxisomal proteins

It has been reported that the West Nile virus (WNV) and DENV infection on A549 and HEK293T cells result in the degradation of peroxisomes [120]. The capsid proteins of both DENV and WNV were reported to interact with the peroxisomal protein Pex19 required for peroxisome biogenesis. Degradation and redistribution of Pex19 from perinuclear region to juxtanuclear region was reported in the infected cells. In addition, reduced level of the antioxidant enzyme catalase was observed in the infected cells. These alterations resulted in an impairment of early antiviral signalling of the peroxisomes.

4.4. Effect on peroxisomal metabolism/enzyme activity

Expression of the PTS containing VP4 protein of the rotavirus, in MA104 cell lines resulted in peroxisomal localization [121]. The role for such a localization was speculated to utilize the peroxisomal lipid metabolism for the supply of cholesterol for lipid raft synthesis, required for the viral replication. Peroxisomal β-oxidation metabolism leads to the production of myristoyl-CoA by shortening the fatty acids chain which could be exported to the cytosol for N-myristoylation of the viral proteins VP2 and VP6 of rotavirus [108].

Studies on HIV suggested an interaction between viral Nef protein and the peroxisomal enzyme thio-esterase using yeast two hybrid system [122]. Further studies reported an increase in the enzymatic activity of human acyl-coA thio-esterase 3 on binding with the Nef protein [123]. The increased activity of the peroxisomal enzyme was speculated to contribute in alteration of the subcellular morphology and in downregulation of the host antiviral response [108].

5. Golgi apparatus

Extensive modifications of proteins for proper functioning and targeting in a cell takes place at the Golgi apparatus. Other functions of Golgi inevitable for the cell are carbohydrate synthesis and lipid transport. The unique stacked structural organization of the Golgi is essential for these functions (Fig. 1).

5.1. Localization of viral proteins to golgi body

The golgi apparatus is composed of three regions namely *cis* golgi network (CGN), medial and *trans* golgi network (TGN). Various viruses and viral proteins have been identified to localize to these golgi regions during their life cycle. For example, HeLa cells upon infection with adeno-associated virus type 5 (AAV-5) led to an accumulation of the viral particles in the TGN and in the golgi-network associated coated vesicles [124]. In SARS- CoV, the transmembrane domain of the ORF7B protein contains the retention signal required for accumulation of the protein in the CGN and TGN [125]. Reports suggest bunyaviruses assemble in the Golgi as a result of its retention signal in the glycoprotein (Gn) of the virus [82,126].

5.2. Effect on the morphology of golgi body

Fragmentation of golgi body is a common phenomenon that occurs as a result of various viral infections (Fig. 2). Orf virus (a parapox virus) causes disruption and fragmentation of golgi in Vero cells. This structural modification affects the late vesicular export machinery and results in downregulation of the host immune response [127]. Similar phenomenon was also reported upon expression of 3C protease of foot-and-mouth disease virus in Vero cells [128]. Infection of HRV1A on WI-38, 293T, and H1-HeLa cells was reported to induce fragmentation of golgi body, rearrangement of the golgi membranes into vesicles which are utilized as sites of RNA replication [129]. Another incidence of the virus induced golgi body fragmentation was observed upon infection of SARS-CoV that resulted in death of Vero cells [130].

Many RNA viruses were also found to alter the integrity of Golgi complex of the host cells. For example, the expression of N-terminal non-structural protein of Norwalk virus in Crandell-Rees feline kidney (CRFK) and HeLa cells co-localizes to Golgi complex and induces its disassembly into discrete aggregates [131]. Another example is the PV infection on Vero cells which results in complete disruption of the CGN into fragments scattered throughout the cytoplasm. The expression of PV protein 2B in Vero, normal rat kidney (NRK) and COS-7 cells also resulted in Golgi bodies disassembly [132]. Similarly, expression of protein 3A of avian encephalomyelitis virus (AEV) in chick embryo brain (CEB) cells and COS-7 cells resulted in depletion of Golgi stacks and in severe disassembly of Golgi bodies [133].

An interesting alteration in the morphology of golgi apparatus was observed upon infection of Turnip Mosaic Virus (TuMV) on *N. benthamiana* plant. TuMV infection was observed to induce amalgamation of golgi apparatus, ER and chloroplast [134]. Poxvirus infection on HeLa cells, BSC-40 monkey kidney cells, and McCoy mouse fibroblast cells led to accumulation of golgin-97 a TGN resident protein in the viral factories [135]. Similarly, 3A protein of some picornaviruses were also found to interact with a Golgi apparatus resident protein namely golgi adaptor protein acyl coenzyme A (acyl-CoA) binding domain protein 3 (ACBD3/GPC60), acts as an adaptor to recruit phosphatidylinositol 4-kinase class III beta (PI4KIII) in infected cells [136]. Evidence shows that the tomato spotted wilt virus (TSWV) glycoprotein Gn localizes to Golgi membranes and induces deformation of the membranes into pseudo-circular and pleomorphic structures in tobacco plant cells [137]. Upon infection of HeLa cells, rabbit kidney cells and mouse monocytes-macrophages cell lines with VACV, viral progeny becomes enwrapped in the membrane derived from TGN cisterna to form the enveloped virus [138].

5.3. Post translational modification of viral proteins

Several viral proteins localize to the golgi body and mature by undergoing post translational modifications such as glycosylation, phosphorylation, *etc*. Rubella virus was reported to undergo a golgi dependent maturation upon infection of BHK-21 and Vero cells [139]. The inner tegument protein pUL37 of the DNA virus HSV was identified to be responsible in directing the viral capsids to the TGN in order to undergo secondary envelopment in different cell lines [140]. The glycoproteins of Bunyamwera virus undergo primary maturation by modifying their sugar composition in the TGN upon infection of the BHK-21 and Vero cells [141].

6. Lipid droplets

Lipid droplets are single membrane bound organelles with a lipid core that primarily consists of neutral lipids like triacylglycerols (Fig. 1). They are essential for lipid storage and metabolism in a cell. These stored lipids can be used to generate and maintain energy homeostasis and hence they are central to the cellular function.

6.1. Localization of viral proteins to lipid droplets

Lipid droplets are dynamic intracellular organelles which are required for storing lipids in a cell. They play a major role in energy homeostasis and membrane trafficking [142]. Many RNA viruses exploit this energy storing capacity of lipid droplets to facilitate their replication [142]. Upon expression, various viral proteins are reported to localize to the lipid droplets [143]. For example, upon HCV infection, the HCV NS5A protein localizes to the surface of the lipid droplets with the help of a host factor diacylglycerol acyltransferase 1 (DGAT1) in Huh7 and HEK293T cells [143]. Another study reported that HCV core 3A protein is involved in downregulating the expression of phosphoinositide 3-kinase (PI3K)/phosphatase and tensin (PTEN) which in turn induces the accumulation of enlarged lipid droplets in human Huh7 and HepG2 cells [144]. In another example, DENV C protein was reported to bind and interact with perilipin 3 a protein present on the surface of the lipid droplets in HepG2 cell lines [145]. A similar localization of DENV C protein was also observed upon infection of DENV2 in BHK-21, HepG2, and C6/36 HT mosquito cells of *A. albopictus* [146]. Additionally, the DENV C protein localization on lipid droplets was also found to be essential for the DENV2 replication [146].

6.2. Effect on lipid droplet content and number

DENV induces autophagy and results in a reduction in lipid droplet area in Huh7.5 cells, a subline derived from Huh7 cells [147,148]. Further analysis of the infected cells showed reduced levels of triglycerides in the lipid droplets and suggests that ATP generation by β-oxidation of fatty acids is essential for robust replication of viral RNA [147,148]. Another study reports that rotavirus recruits lipid droplets into their viroplasm compartments upon infection of MA104, Caco-2, BSC-1, and Cos-7 cell lines [149]. Confocal microscopy studies reported that two LD-associated proteins namely perilipin A and ADRP colocalize with rotaviral proteins present in the viroplasm [149]. Overexpression of the HBV X (HBx) protein was found to induce lipid accumulation in hepatic cells [150,151]. Na and colleagues found that HBx induces a pathway that involves the expression of Liver X receptor and its associated genes result in accumulation of lipid droplets in HepG2 cell lines [152].

7. Lysosomes and vacuoles

Lysosomes are single membrane-bound organelles which house enzymes involved in the degradation of various extracellular and intracellular macromolecules such as proteins, pathogens, *etc* through phagocytic or autophagic pathway. Plant and fungal vacuoles have similar degradative and storage functions like the lysosomes (Fig. 1). The specialized acidic lumen is the unique feature of these organelles which is needed to keep the enzymes active.

7.1. Recruitment of lysosomal enzymes

Viruses utilize lysosomal enzymes in order to facilitate their replication and release within the host cell [153]. It has been suggested that lysosomal enzymes are involved at different stages of VACV and mouse hepatitis virus replication [153]. They proposed a possibility for viruses to recruit lysosomal enzymes inside phagosomes in order to uncoat and release their genome in the host cell. A possible role for the lysosomal enzymes in enhancement of glycolysis in viral infected cells was also proposed. Recent studies reported the accumulation of HAV progeny in the lysosome of the host HepG2 cells. The maturation of these viral particles was reported to be catalysed by the lysosomal protease [154]. SV40 infection in BSC-1 and 3T3 cell lines resulted in swelling up of lysosomes followed by the release of lysosomal enzyme into the cytoplasm [155].

7.2. Other lysosomal alterations

Since lysosomes play a major role in the host's antiviral response, they are likely to become a target for certain viruses. The X protein of the HBV leads to inhibition of lysosomal acidification leading to loss of functioning [156]. However, the lysosome's ability to fuse with autophagosomes was found to remain unaffected. This virus induced accumulation of immature lysosomes resulting in the suppression of autophagic degradation was followed by development of HBV-associated hepatocellular carcinoma [156]. Deglycosylation of the lysosome-associated membrane proteins by neuraminidase (NA) of H5N1 influenza virus resulted in destruction of lysosomes. This was followed by cell death due to the release of hydrolytic lysosomal enzymes to the cytoplasm [157]. Shubin and colleagues studied the expression of 3C protease of HAV in A549 and human lung epidermoid carcinoma (Calu-1) cell lines and found that HAV 3C protease induces the development of non-acidic cytoplasmic vacuoles which originate from several types of lysosomal/endosomal organelles [158]. Similarly several viruses like HIV, adenovirus, PV have been reported to cause lysosomal rupture [159].

7.3. Morphological alterations of vacuole

Tobacco plant when infected with cucumber mosaic virus (CMV), the viral replicase complex that constitutes the replicase-associated protein CMV1a and RNA dependent RNA polymerase protein CMV2a was reported to localize on the vacuolar membrane [160]. Singapore grouper iridovirus (SGIV) infection on grouper embryonic cells (GECs) from the brown-spotted grouper *Epinephelus tauvina* results in the formation of a large intracellular vacuole for viral accumulation. Later, the virus recruits the host cytosolic membrane-bending proteins in order to induce tubulation of vacuolar membrane [161]. The individual vacuoles fuse together to form a large vacuole which in turn fuses with the cell membrane. These events aid in the release of virions [161].

7.4. Vacuole acidification

Semliki Forest Virus (SFV) targets the vacuolar ATPase in order to cause acidification of vacuoles resulting in low intra luminal pH [162]. Upon infection with the SFV the endocytic vacuoles with low pH trigger membrane fusion essential for the viral pathogenesis in BHK-21 cells [163]. Vacuolar proton ATPase activity leading to low intra endosomal pH was reported to be required for the entry of reovirus into the host cells [164]. Acidification of vacuoles by cellular V-ATPase in human dermal fibroblast cells upon infection of HCMV was reported to be required for the formation of the specialized compartment for virion assembly [165].

8. Other compartments

Apart from the above discussed well defined organelles of a cell, viruses also modify and hijack various vesicular structures and protein complexes of the host cell to ensure efficient infection. We discuss these essential compartments/structures in this section. Endosomes are required for internalization of extracellular material into the cells and lead them to lysosomes for degradation or recycle back to the plasma membrane. Multi vesicular bodies are vesicular compartment of the endocytic pathway and contain intraluminal vesicles. Autophagosomes are double membrane vesicular structures that sequester the cytoplasm containing proteins, organelles, *etc* and direct them to degradation (Fig. 1).

8.1. Endosomes

Efficient cellular entry of most viruses is via endocytic pathway that comprises of various endosomes. Several viruses like influenza, SFV, VSV, SV40, ebola, *etc* use different endocytic pathways like clathrin, caveoli or micropinocytosis to gain entry into the cells [6,166–168]. Viruses modify or induce the formation of vesicles like endosomes in order to facilitate their multiplication inside the host cells [169]. SFV modifies the endosomal and lysosomal membrane of the infected BHK-21 cells for the construction of its replication site [170]. Further the endosomes and lysosomes were reported to fuse together resulting in the formation of cytoplasmic vacuoles [170]. SV40 was reported to trigger the formation of endocytic vacuoles that migrate and fuse with the nuclear membrane upon infection of CV-1 cells leading to the migration of virions into the infected cell nucleus [171,172].

8.2. Multivesicular bodies

Endosomal sorting complexes required for transport (ESCRT) catalyse the process of invagination of endosomal membrane and result in the formation of multiple vesicular bodies (MVB) in eukaryotic cells [173]. MVB act as an intermediate for transporting ubiquitinated or misfolded protein to lysosomes [173]. MVB are also reported to play an active role in endolysosomal transport and budding of the virus. Several RNA and DNA viruses hijack the ESCRT machinery in order to facilitate their release from the infected cells [169]. The matrix protein VP40 recruits TSG101 protein and ESCRT-1 complex constituting of VPS28, VPS37B and VPS4 in order to direct the ebola virus into multivesicular bodies that assists in their budding [174]. Hoffmann and colleagues reported that upon infection of hepatoma derived cell lines by the DNA virus HBV, cellular α-taxilin acts as an adaptor for the binding of large HBV surface antigen with ESCRT components. This aids in recruiting the ESCRT machinery for the release of HBV-DNA containing particles [175].

8.3. Autophagosomes

Various RNA viruses alter autophagosomes and induce or suppress autophagy in order to complete their life cycle or to escape from the host antiviral response [176]. It has been reported that the coxsackie B3 infection triggers the formation of autophagosomes in HeLa and HEK293 cells [177]. Prevention of lysosomal fusion with autophagosomes also enhanced coxsackie virus replication in the host cells. Wild type mouse embryonic fibroblast (MEF) and Huh7 cells also exhibit enhanced autophagosome formation upon DENV 2 infection [178]. The viruses modulating the phenomenon of cellular autophagy for their advantage have been reviewed elsewhere [176].

8.4. Host ubiquitin proteasome system (UPS)

Proteasome is a complex of proteases that selectively degrades intracellular proteins. This complex is tightly regulated and identifies polyubiquitinated proteins for degradation process. Recent studies identified that viruses hijack UPS in several ways to enhance their infectivity [179]. This is achieved by degradation of host proteins of UPS, enhancing the function of viral proteins by modifications, hampering the modifications of signalling molecules of innate immunity, *etc* [179]. Virus induced ubiquitination and subsequent proteasomal degradation of p53 as a strategy is employed by DNA viruses such as HPV, AdV, *etc* [180]. Viral protein X of HIV-2 was reported to be responsible for the ubiquitination and proteasomal degradation of the host protein SAMHD1 that inhibits HIV infection [181]. An interesting strategy by DenV was reported where the viral protein NS5 stimulates proteasomal degradation of STAT2 and blocks type 1 IFN signalling and thus evades the host immune mechanisms [182]. Similarly selective degradation of NS3 (non-structural protein) of the Zika virus via proteasome mediated pathway was recently reported [183]. This proteasome dependant degradation of the viral protein was proposed as a strategy for the host antiviral mechanism.

A role for UPS has also been reported in plant viral infections. Components of RNA silencing such as ARGONAUTE 1 are targeted to proteasomal degradation by viruses like Potato virus X, Enamovirus, *etc* for efficient infection [184,185].

9. Conclusions

This review summarizes the modifications that organelles encounter upon viral infection in a cell. Understanding organelle dynamics under various conditions is a fundamental question that has attracted researchers for a long time. The importance of organelle dynamics and function is highlighted by many examples of diseases/disorders where it is affected. Alterations in organelles such as shape, content, dynamics and eventually the function as a result of viral infections is observed. Not only viruses but pathogenic bacteria have also been reported to alter organelles for their survival and infection. As emphasized in this paper, recent studies have shown that many viruses encode proteins that are targeted to various cellular organelles and control their functions. Certainly there exists a close relationship between organelle dynamics and viral infections but thorough characterization will highlight their relevance to pathogenesis. Advanced methods in microscopy and proteomics have enabled such characterization and the molecular details of virus-host interactions and viral replication in host cells is now understood in detail for few viruses. It is important to determine how various organelle proteins are temporally and spatially regulated upon viral infections leading to altered functions. Organelles not as independent entities but a role for inter-organelle communication/inter-organelle cross talk in a cell for optimum functioning is now unequivocally accepted. This is another very interesting aspect to be explored to enhance our understanding of the virus-host interaction mechanisms to enable design of new antiviral strategies. Our understanding on the organelle-virus interaction has been rapidly increasing with the advent of new molecular biology tools and advance imaging techniques. Although we know the basic modus operandi of the viruses, there might be a novel virus that behaves different than the existing dogma with respect to host cellular architecture.

Conflict of interest

The authors declare to no conflict of interest.

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