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Variant Cells and Viral Infections: Understanding Cellular Coping Mechanisms

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ABSTRACT

Cellular stress, induced by diverse factors including viral infection, reactive oxygen species (ROS), hypoxia, and toxin exposure, disrupts normal cellular function. The endoplasmic reticulum (ER) is pivotal in managing cellular stress, notably through the unfolded protein response (UPR) and ER-associated degradation (ERAD) pathways. This intricate process involves a complex interplay of transcription factors and signaling molecules. During viral infection, cells activate a multifaceted antiviral response, which is specifically modulated by both the virus type and the molecular mechanisms of the host's immune system. For instance, certain viruses like Japanese encephalitis virus (JEV) exploit multiple cellular pathways for replication and propagation. Viral infection can significantly impact cellular processes like autophagy and apoptosis, either promoting or suppressing these pathways. Thus, the cellular response to viral infection represents a dynamic interplay that can either benefit the host or be exploited by the virus for its propagation. For instance, viruses within the *Flaviviridae* family often preserve host cell viability during early infection to enhance replication, subsequently triggering apoptosis or other cell death mechanisms to facilitate viral dissemination. This review explores the diverse responses of infected cells to various viruses, highlighting the complex molecular strategies employed by both host and pathogen.

INTRODUCTION

The endoplasmic reticulum (ER) is a multifunctional organelle in eukaryotic cells critical for the synthesis, folding, and transport of proteins, lipids, and membranes components. A variety of cellular stressors, including hypoxia, exposure to toxins (such as toxic chemical compounds and ultraviolet radiation), nutrient deprivation, ROS, and viral infection, can disrupt ER function. Maintaining calcium homeostasis is essential for proper ER function. Cells tightly regulate cytoplasmic free cytosolic calcium concentrations at approximately 100 nM through buffering and distribution between the ER and mitochondria. Excessive mitochondrial calcium accumulation can trigger the opening of the mitochondrial permeability transition pore, ultimately leading to apoptosis and necrosis [1]. Disruption of ER calcium homeostasis can impair protein folding, resulting in the accumulation of misfolded proteins within the ER lumen, which further exacerbates ER stress [2].

The ER mitigates stress through the unfolded protein response (UPR), a multifaceted signaling pathway that aims to restore ER homeostasis. The UPR involves two key mechanisms: (1) attenuating protein translation to lessen ER workload, and (2) transcriptionally activating genes that encode ER chaperones, folding enzymes, and components of the ER-associated degradation (ERAD) system. These coordinated responses increase protein folding capacity and target misfolded proteins for degradation. Three key ER-resident transmembrane proteins sense ER stress and initiate distinct UPR signaling branches: the activating transcription factor 6 (ATF6), the inositol-requiring enzyme 1α (IRE1α), and the protein kinase RNA-like endoplasmic reticulum kinase (PERK) [3, 4].

The interaction between ER stress sensors and the binding immunoglobulin protein (BiP), also known as glucose-regulated protein 78 (GRP78), is disrupted in the presence of accumulating misfolded proteins, leading to the activation of these sensors. For instance, eukaryotic initiation factor 2α (eIF2α) is phosphorylated by PERK, reducing protein translation and facilitating the expression of genes regulated by the UPR, including those involved in ERAD and autophagy. BiP, a member of the Hsp70

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family, is a resident ER chaperone and a key regulator of UPR activation [5]. Upon ER stress, BiP dissociates from ATF6, which then translocates to the Golgi apparatus for proteolytic cleavage. The released N-terminal fragment of ATF6 then is transported from the Golgi to the nucleus and activates the expression of UPR target genes, including those encoding X-box binding protein 1 (XBP1) and ER chaperones.

Unlike PERK and IRE1α, which mainly control translation and gene expression, ATF6 directly contributes to protein quality control by regulating both the degradation of misfolded proteins and enhancing protein folding capacity. This crucial role of ATF6 in ER stress resistance is evident in mice, where homozygous deletion of ATF6 leads to embryonic lethality in mice [6]. Expanding on the roles of these sensors, while PERK and IRE1α share some structural and functional similarities, their downstream signaling pathways and cellular outcomes can differ. For instance, the initial activation of IRE1α signaling promotes cell survival by facilitating the splicing of X-box binding protein 1 (XBP1) mRNA, which leads to the production of a potent transcription factor that upregulates genes involved in ER stress mitigation and protein folding. However, sustained IRE1α activation can trigger apoptosis, a process potentially mediated through its interaction with tumor necrosis factor receptor-associated factor 2 (TRAF2).

Apoptosis is a highly regulated process of programmed cell death that facilitates the removal of damaged or unnecessary cells. Two primary pathways lead to apoptosis: the extrinsic pathway, activated by death receptors on the cell surface, and the intrinsic pathway, initiated by internal stress signals, often linked to mitochondrial dysfunction [7]. Although distinct in their initiation, these pathways ultimately converge to activate a cascade of proteolytic enzymes called caspases, leading to the systematic degradation of cellular components [8]. In addition to these general pathways, specific stress responses like prolonged IRE1α activation and its interaction with TRAF2 can initiate apoptotic pathways through the activation of apoptosis signal-regulating kinase 1 (ASK1) and c-Jun NH2 terminal kinase (JNK), ultimately contributing to cell death [9].

C/EBP homologous protein (CHOP), a downstream effector of the PERK pathway, mediates both apoptosis and the regulation of B-cell lymphoma (Bcl-2) family proteins during ER stress. The Bcl-2 family includes anti-apoptotic members like Bcl-2 and Bcl-xL, which maintain mitochondrial integrity, and pro-apoptotic members, which are further categorized into multidomain proteins (*e.g.*, BAK, BAX) and BH3-only proteins (*e.g.*, BID, BAD, NOXA, PUMA) [10]. BH3-only proteins, which are often upregulated by stress signals, can inhibit anti-apoptotic Bcl-2 family members or directly activate BAK and BAX, thereby facilitating apoptosis [11].

Autophagy, a highly conserved catabolic process, is integral to cellular homeostasis through the degradation and recycling of damaged organelles, protein aggregates, and intracellular pathogens [12, 13]. This process is essential for maintaining cellular health and defending against invading pathogens, including viruses. However, viruses have acquired mechanisms to manipulate cellular pathways, including apoptosis, autophagy, and the UPR, to facilitate their own replication and survival within infected cells and tissues [14]. Beclin-1, a key regulator of autophagy, exemplifies the intricate interplay between apoptosis and autophagy. This protein contains a BH3 domain that mediates its interaction with both cellular and viral anti-apoptotic Bcl-2 family members. Upon autophagy induction, Beclin-1 interacts with the class III phosphatidylinositol 3-kinase (PI3KC3) complex to generate phosphatidylinositol 3-phosphate (PI3P) on the phagophore membrane, which recruits autophagy effectors for autophagosome formation and maturation [15]. Focusing on RNA and DNA viruses, excluding coronaviruses due to their unique mechanisms, we examine how these pathogens exploit or circumvent cellular coping mechanisms, providing insights into the intricate interplay between viral infection and cellular responses. Building on these cellular mechanisms, this review explores how the inherent heterogeneity of cellular populations, even within a single tissue, influences these interactions. Cells exhibit a spectrum of responses to viral infection, with variations in ER stress susceptibility, autophagy efficiency, and apoptotic thresholds. This cellular diversity not only influences viral tropism but also the effectiveness of viral replication strategies, where viruses may adapt to or benefit from the variability in cellular stress responses. This cellular diversity can be attributed to factors like cell type, differentiation state, and microenvironment. Viruses, in turn, can exploit this heterogeneity, preferentially targeting more susceptible cells or manipulating specific cell populations to establish a permissive environment for replication. Understanding the dynamic interplay between viral infection and cellular heterogeneity, particularly in the context of ER stress, autophagy, and apoptosis, is paramount for developing effective antiviral therapies that can mitigate viral pathogenesis while minimizing host cell damage.

Cellular responses to RNA viral infections

Hepatitis C virus (HCV) infection poses a significant challenge to global health, commonly leading to chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). HCV, along with hepatitis B virus (HBV), can induce ER stress and subsequent calcium release from the ER in infected hepatocytes [16]. Disruption of calcium homeostasis can lead to divergent cellular outcomes: elevated cytosolic calcium activates calpains, promoting apoptosis, while also activating AMPK, which inhibits mTOR and thus induces autophagy. Furthermore, viral infection often triggers a multifaceted stress response involving both an initial innate immune response,

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characterized by interferon production stimulated by viral double-stranded RNA (dsRNA), followed by ER stress induced by the accumulation of viral proteins [17]. Viral proteins can bind to BiP, thereby preventing it from binding to and inhibiting PERK, ATF6, and IRE1α, leading to the activation of these ER stress sensors (Figure 1).

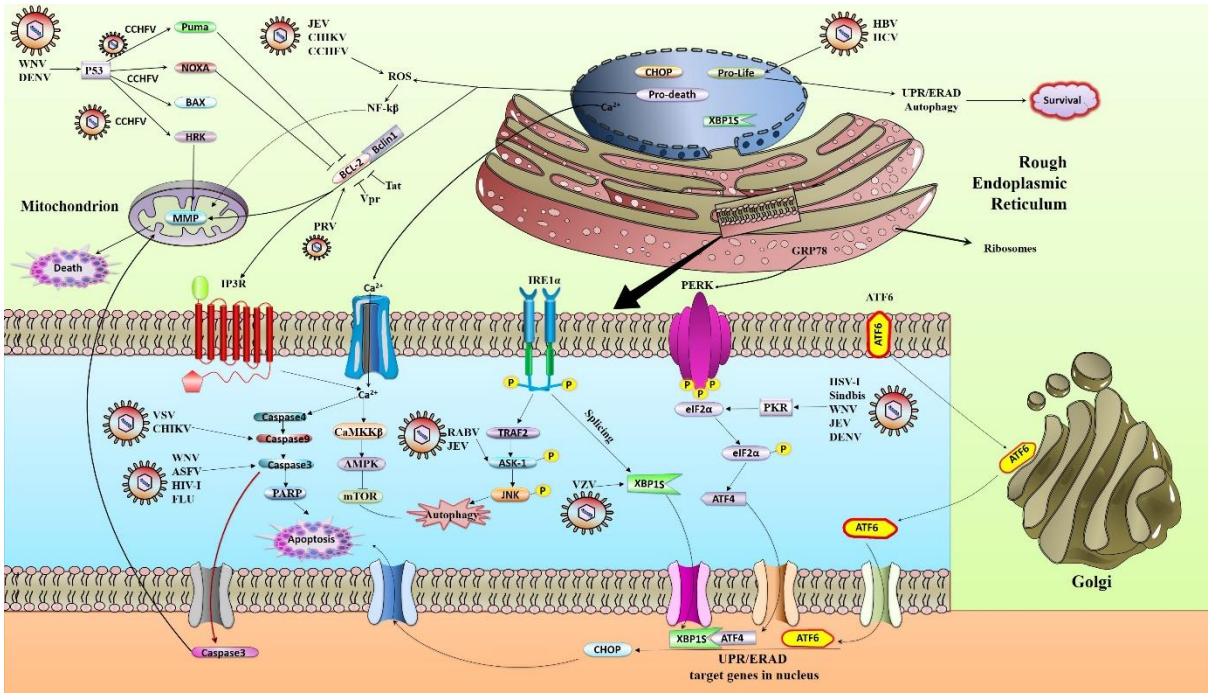


Fig. 1. The endoplasmic reticulum response to stress is mediated by UPR / ERAD pathway. This pathway also intersects with autophagy, apoptosis, and calcium homeostasis. The mechanisms of some viruses' actions in the host cell and the organelles they affect can be seen in this figure. Several viruses employed two or more mechanisms to affect many important organelles of host cells. If one of the multiple mechanisms of virus penetration is blocked by host cells' defense system, the survival and reproduction of viruses is ensured by its other mechanisms (Created with BioRender.com).

Dengue viruses (DENVs) exemplify how viruses manipulate cellular stress responses. These viruses can evade host immunity, facilitate their own replication, and modulate autophagy through the strategic manipulation of the UPR [18]. DENV infection triggers a temporally controlled UPR, with each branch activated at a distinct phase of the viral life cycle: PERK-dependent eIF2α phosphorylation dominates early in infection, followed by IRE1-XBP1 activation during mid-infection, and finally, ATF6 activation in the later stages [19]. Interestingly, DENV can selectively inhibit apoptotic mediators downstream of the IRE1-XBP1 pathway, effectively promoting cell survival to establish a more favorable environment for viral replication [19]. Additionally, DENV infection activates ataxia-telangiectasia mutated (ATM) kinase signaling, which further inhibits mTOR, activates the PERK pathway, and enhances autophagy, thereby promoting viral replication [20]. This coordinated manipulation of ER stress and autophagy highlights the complex interplay between viral infection and cellular responses.

Zika virus (ZIKV) infection is associated with significant health risks, particularly due to its potential to cause severe neurological complications, including microcephaly in newborns. ZIKV infection has been demonstrated to induce significant ER stress across various cell types, including neuronal precursors, astrocytes, skin fibroblasts, and epithelial cells, which often display characteristic ER stress markers, such as the upregulation of chaperones like calreticulin and calnexin, and the formation of large ER-derived vacuoles [21, 22]. This ER stress response contributes to both viral pathogenesis and the host immune response. For instance, ER stress in ZIKV-infected neuronal precursors has been implicated in cell death and microcephaly development [21]. Moreover, ZIKV-infected cells can release factors that modulate UPR activity in neighboring cells, potentially amplifying the antiviral response or facilitating viral spread. While some studies suggest that ZIKV may induce cell cycle arrest as an antiviral defense mechanism [23], others have demonstrated that ZIKV can exploit UPR signaling to promote its own replication. ZIKV infection activates the tyrosine kinase receptor in microglia, subsequently leading to the activation of IRE1α-XBP1 and ATF6 pathways [24, 25]. Furthermore, ZIKV infection of astrocytes triggers the production of chemokines and cytokines, primarily mediated through UPR activation. This reliance on the UPR is likely due to

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the fact that ZIKV effectively inhibits interferon (IFN)-regulated cytokine signaling pathways, which is crucial for cytokine signaling, such as the JAK1/STAT3 pathway (Figure 1) [26, 27].

Human immunodeficiency virus (HIV) infection presents a complex interplay between viral manipulation and host cellular responses. During the early stages of infection, HIV inhibits the later stages of autophagy, specifically autophagosome maturation, a mechanism that promotes its own replication. The HIV-1 protein Nef disrupts autophagosome-lysosome fusion by binding to beclin-1, thereby sequestering transcription factor EB (TFEB) in the cytosol [28]. This sequestration of TFEB, a master regulator of lysosomal biogenesis, further impairs autophagy and facilitates viral persistence. In addition to its effects on autophagy, HIV infection also triggers a multifaceted ER stress response. The virus induces PERK activation, leading to eIF2α phosphorylation and subsequent inhibition of protein translation, which can predispose infected cells to undergo caspase-3 (CASP3)-dependent apoptosis [29]. HIV infection also activates the IRE1 pathway, promoting the expression of ER stress-responsive genes, and induces ATF6 cleavage, leading to increased expression of the chaperone BiP (Figure 1).

Vesicular stomatitis virus (VSV) infection triggers a complex interplay between apoptotic pathways and autophagy. Wild-type VSV infection typically induces apoptosis through the intrinsic mitochondrial pathway, involving CASP9 activation, this response is often associated with the inhibition of viral replication. However, VSV carrying mutations in its matrix protein or glycoprotein can suppress host gene expression [30] and trigger apoptosis through the extrinsic pathway, activating CASP8 via death receptor signaling [31]. In parallel to these apoptotic mechanisms, autophagy serves as a key mechanism in antiviral immunity as it delivers viral components, such as nucleic acids, to endosomal compartments containing Toll-like receptors (TLRs), which initiates innate immune signaling. Notably, pharmacological inhibition of autophagy or genetic deletion of ATG5 impairs the recognition of VSV and Sendai virus by TLR-7, further highlighting the importance of autophagy in antiviral responses [32].

The role of autophagy in West Nile virus (WNV) infection is not fully understood. While some studies suggest that WNV replication is independent of autophagy [33], others have reported that WNV infection can upregulate autophagy in specific cell lines [34]. This variation may reflect cell type-specific differences or variations in experimental conditions. WNV replication can be inhibited by apoptosis, particularly during the early stages of infection, similar to other flaviviruses like Japanese encephalitis virus and DENV. To evade this host defense mechanism, these viruses have developed mechanisms to interfere with apoptotic pathways, often by activating pro-survival signaling cascades. For instance, WNV activates the phosphoinositide 3-kinase (PI3K)/AKT pathway, which inhibits apoptosis, thereby promoting cell survival and enhancing viral replication [35, 36]. WNV infection also elicits a complex ER stress response. While the XBP1 pathway appears dispensable for WNV replication, the virus induces proteasomal degradation of ATF6 and activates the PERK pathway, leading to eIF2α phosphorylation and CHOP expression (Figure 1) [37].

Chikungunya virus (CHIKV) infection highlights the intricate interplay between autophagy and apoptosis during viral infection. CHIKV-induced autophagy initially delays caspase-dependent apoptosis, potentially through the activation of the IRE1α-XBP1 pathway and the suppression of ROS-mediated mTOR inhibition. However, as viral replication progresses, CHIKV suppresses autophagy, possibly to promote cell survival and maximize viral progeny production. Notably, the use of autophagy inducers has shown promise in limiting the severity of acute Chikungunya disease, indicating a protective role for autophagy in this context [38]. Moving from CHIKV to another arbovirus, Crimean-Congo hemorrhagic fever virus (CCHFV) infection also triggers a complex interplay between ER stress and apoptosis. CCHFV infection can induce massive liver necrosis, characterized by prominent cytopathic effects and elevated levels of the ER stress marker CHOP in hepatocytes [39]. This demonstrates the critical role of ER stress in CCHFV-induced liver pathology. Furthermore, CCHFV activates both the intrinsic mitochondrial and extrinsic death receptor pathways of apoptosis, further contributing to its pathogenesis (Figure 1) [39].

The interaction between rabies virus (RABV) infection and cellular stress responses is not fully understood. While some studies indicate that attenuated RABV strains can induce apoptosis, the underlying mechanisms and the role of ER stress are poorly understood [40, 41]. Interestingly, a study by Liu *et al*. (2017) revealed that the phosphoproteins of two attenuated RABV strains (HEP-Flury and CVS-11) bind to beclin-1, thereby inhibiting autophagosome maturation through a CASP2-mediated mechanism. This interference with autophagy was found to facilitate viral genome replication, indicating a strategy by RABV to circumvent cellular defenses [42]. However, it is crucial to note that these findings were obtained using attenuated vaccine strains, which may differ significantly from circulating wild-type RABV strains in their interactions with host cells.

Research in RABV-infected mice has revealed that infection with wild-type RABV, particularly street rabies virus (SRABV), triggers a complex interplay between ER stress, autophagy, and apoptosis. SRABV infection leads to increased expression of ER stress markers, including mRNAs for ASK1, ATF6, and CHOP, along with autophagy-related proteins like beclin-1 [43, 44]. This ER stress response is accompanied by an attempt at cellular recovery through autophagy, which, however, transitions towards apoptosis as the infection advances. Specifically,

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SRABV infection activates the IRE1α pathway, leading to increased ASK1 expression and subsequent autophagy induction. The accumulation of misfolded proteins during SRABV infection also triggers the upregulation of GRP78, which activates ATF6 and initiates the unfolded protein response (UPR). The increase in CHOP expression likely results from the activation of both the PERK/eIF2α and IRE1α pathways, further exacerbating ER stress. However, a significant increase in CASP3 expression, a marker of apoptosis, was observed only in infected mice treated with beclin-1 [44]. This indicates that while SRABV-induced autophagy may initially promote cell survival, it can ultimately make infected cells more susceptible to apoptosis. Overall, SRABV infection appears to exploit the UPR/ERAD pathway, initially promoting cell survival through autophagy, but ultimately leading to apoptosis as the infection progresses [45].

Influenza A virus (IAV), a significant human respiratory pathogen, manipulates cellular stress responses to facilitate its replication cycle. Early studies in lung epithelial cells demonstrated that IAV infection primarily activates the IRE1 pathway of the UPR, leading to XBP-1 mRNA splicing, with minimal impact on the PERK and ATF6 pathways [46]. This selective activation suggests a specific role for the IRE1-XBP1 axis in IAV infection. IAV infection activates the NLRP3 inflammasome, leading to mitochondrial damage, ROS production, and the formation of the inflammasome complex, which includes NLRP3, ASC, and caspase-1. This complex promotes the maturation of pro-inflammatory cytokines, contributing to the inflammatory response characteristic of IAV infection [47]. Following its influence on autophagy, IAV exhibits a biphasic modulation of apoptosis. During early infection, IAV suppresses apoptosis by downregulating pro-apoptotic proteins like BAX and BAK. However, in later stages, the virus promotes apoptosis by upregulating BAX and BAK, activating pro-apoptotic proteins (BAD, BID), and inducing PARP-1 cleavage, while downregulating the anti-apoptotic protein Bcl-2 [48]. This shift towards pro-apoptotic activity facilitates viral dissemination. IAV also modulates cellular factors like p53 and interferes with host ubiquitin ligase activity, highlighting the multifaceted strategies employed by this virus to manipulate cellular processes (Figure 1) [49].

RNA viruses have evolved diverse strategies to facilitate their survival and replication within hosts by manipulating cellular coping mechanisms. These viral strategies enable evasion of host immune responses, establishment of persistent infections, and promotion of viral dissemination. As highlighted in the examples above, these strategies involve intricate interactions with the UPR, apoptosis pathways, and autophagy. Understanding these interactions is essential for the development of novel antiviral strategies to alleviate the health impact of these pervasive pathogens.

Changes in host cells due to infection with DNA virus

HBeAg-positive HBV patients often experience chronic infection. In these patients, large HBV surface antigen (LHB) mutants, pre-S1 and pre-S2, accumulate in the ER, evading immune surveillance and triggering ER stress. This ER stress leads to oxidative DNA damage and genomic instability, ultimately contributing to hepatocellular carcinoma (HCC) development. The hepatitis B virus X protein can activate the ATF6 and IRE1-XBP1 pathways of the unfolded protein response [50]. Similarly, infection with pseudorabies virus (PRV) also induces ER stress. Yang *et al*. (2019) showed upregulated expression of a marker of ER stress, GRP78, during PRV infection, correlating with the activation of the IRE1-XBP1 and eIF2α-ATF4 pathways [51]. Their study also showed that PRV infection disrupts ER homeostasis, activates the CHOP-Bcl2 pathway, and thereby induces apoptosis in the final stages of infection (Figure 1).

Herpes simplex virus 1 (HSV-1) manipulates host cell responses, including autophagy. The viral protein ICP34.5 inhibits host antiviral mechanisms by preventing autophagy via two pathways: directly by binding to beclin-1, a key autophagy regulator, and indirectly by inhibiting PKR-mediated autophagy induction [52]. Autophagy also plays a crucial role in the adaptive immune response to viral infections. Moreover, Lee *et al*. (2010) [53] demonstrated that mice deficient in Atg5 specifically in CD11c+ dendritic cells exhibited impaired CD4+ T cell priming against hepatitis C virus (HCV) infection, leading to increased mortality. This finding highlighted the importance of autophagy in antigen presentation by dendritic cells and subsequent T cell activation. The interplay between autophagy and innate recognition of viruses was first elucidated in plasmacytoid dendritic cells [54].

Varicella-zoster virus (VZV) infection indicates that autophagy is involved in the VZV life cycle through the presence of the VZV IE62 nuclear protein in infected vesicular cells. VZV infection leads to ER lumen enlargement and significant increases in XBP1 and CHOP protein levels. XBP1 mRNA is regulated by ATF6 and spliced by IRE1, an ER stress sensor. The induction of CHOP is indicative of chronic ER stress, which can contribute to stress-mediated apoptosis and the regulation of mitochondrial oxidative stress. In contrast to other viruses, VZV does not appear to express autophagy-inhibiting genes, suggesting that the UPR might help maintain cellular homeostasis during VZV infection by not suppressing autophagy [55].

African swine fever virus (ASFV) infection demonstrates a complex interaction between viral replication and host cell survival by triggering ER stress and apoptosis. ASFV uses the ER as its replication site, activating the ATF6 signaling pathway. This activation leads to the transcriptional upregulation of chaperone-

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encoding genes, which may benefit the virus by facilitating viral protein folding and preventing protein aggregation in the host cell. Furthermore, ASFV infection leads to a rapid increase in ER stress markers like CASP3, CASP9, CASP12, BiP, calreticulin, calnexin, and ERp57 shortly after infection. By modulating the UPR to delay premature apoptosis, ASFV ensures its own efficient replication [56].

These findings demonstrate the diverse strategies DNA viruses use to manipulate host cells' ER and autophagy pathways. These viruses can induce ER stress to improve viral protein folding or trigger apoptosis for viral dissemination. However, some viruses have evolved to evade or suppress these host responses, ensuring their survival and persistence. Understanding this interplay is essential for developing antiviral therapies that target viral replication while minimizing host cell damage.

CONCLUSIONS

Viral infections typically involve a complex interplay between viral propagation and host cell responses, typically involving the induction of cellular stress pathways. The activation of pathways like the unfolded protein response, autophagy, and apoptosis depends on various factors including virus type, host cell, and environmental cues. These pathways can serve both protective and pathogenic roles for the host, as viruses have evolved to manipulate or circumvent them. Thus, novel therapeutic strategies targeting these stress pathways are being explored to disrupt viral replication mechanisms or enhance cellular antiviral defenses. Ongoing research into these interactions is essential to develop effective antiviral therapies that can limit viral replication while minimizing host cell damage.

Further investigation into the complex interplay between viral infection and these fundamental cellular processes could lead to innovative therapeutic strategies that can effectively target viral infections while minimizing detrimental effects on the host.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest associated with this manuscript.

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