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REVIEW ARTICLE

The expanding roles of endoplasmic reticulum stress in virus replication and pathogenesis

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Abstract

The endoplasmic reticulum (ER) is a cellular membrane organelle that plays important roles in virus replication and maturation. Accumulating evidence indicates that virus infection often disturbs ER homeostasis and leads to ER stress, which is associated with a variety of prevalent diseases. To cope with the deleterious effects of virus-induced ER stress, cells activate critical signaling pathways including the unfolded protein response (UPR) and intrinsic mitochondrial apoptosis, which have complex effects on virus replication and pathogenesis. In this review, we present a comprehensive summary of recent research in this field, which revealed that about 36 viruses trigger ER stress and differentially activate ER stress-related signaling pathways. We also highlight the strategies evolved by viruses to modulate ER stress-related signaling networks including immune responses in order to ensure their survival and pathogenesis. Together, the knowledge gained from this field will shed light on unveiling the mechanisms of virus replication and pathogenesis and provide insight for future research as well as antiviral development.

Abbreviations: ER, endoplasmic reticulum; UPR, unfolded protein response; PERK, pancreatic ER kinase (PKR)-like ER kinase; IRE1, inositol-requiring enzyme 1 (IRE1); ATF6, activating transcription factor 6 (ATF6); GRP78, glucose regulated protein 78; eIF2α, the alpha subunit of eukaryotic translation initiation factor-2; ATF4, activating transcription factor-4; GADD34, growth arrest and DNA damage-inducible 34; PP1, protein phosphatase 1; XBP1, X box-binding protein 1; PDI, protein disulphide isomerase; DR5, death receptor-5; TRB3, tribbles-related protein 3; ERO1α, ER oxidase 1α; ROS, reactive oxygen species; PVX, Potato virus X; CHIKV, Chikungunya virus; SFV, Semliki Forest Virus; SINV, Sindbis virus; LCMV, Lymphocytic choromeningitis virus; ASFV, African swine fever virus; RV, Rubella virus; HEV, Hepatitis E virus; BMV, Brome mosaic virus; IPNV, Infectious pancreatic necrosis virus; HN, hemagglutinin-neuraminidase; CCHFV, Crimean-Congo hemorrhagic fever virus; DUGV, Dugbe virus; TULV, Tula virus; MHV, Murine hepatitis virus; IBV, Infectious bronchitis virus; PEDV, porcine epidemic diarrhea virus; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; BVDV, Bovine viral diarrhea virus; DENV, Dengue virus; HCV, Hepatitis C virus; JEV, Japanese encephalitis virus; WNV, West Nile virus; HBV, Hepatitis B virus; HBx, HBV X protein; EBV, Epstein-Barr virus; HSV-1, Herpes simplex virus type 1; HCMV, Human cytomegalovirus; VZV, Varicella Zoster virus; RGNNV, Betanodavirus redspotted grouper nervous necrosis virus; IAV, Influenza A virus; CDV, Canine distemper virus; RSV, Human respiratory syncytial virus; SV5, Simian Virus 5; CVB3, Coxsackievirus B3; RRV, Rhesus rotavirus; HIV, Human immunodeficiency virus; MoMuLV, Moloney murine leukemia virus-TB; FrCas^E, Neurovirulent mouse retrovirus; VSV, Vesicular stomatitis virus; VV, virus vaccinia virus; GFLV, Grapevine fanleaf nepovirus; YFV, Yellow fever virus; PKR, double-stranded RNA-dependent protein kinase (PKR); GCN2, general control non-derepressible-2; MMP, mitochondrial membrane potential; MNV-1, murine norovirus; COS2, cyclo-oxygenase 2; gB, glycoprotein B; CLT, clotrimazole; DRACO, Double-stranded RNA activated caspase oligomerizer

Keywords

Antiviral therapy, apoptosis, ER-to-nucleus signaling pathway, unfolded protein response, virological treatments

History

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Introduction

The ER is an important cellular organelle that controls several critical aspects of cellular processes such as cellular proteins folding and post-translational modifications. It also plays pivotal roles in viral infection processes. As intracellular parasites, viruses must utilize the ER to complete some of

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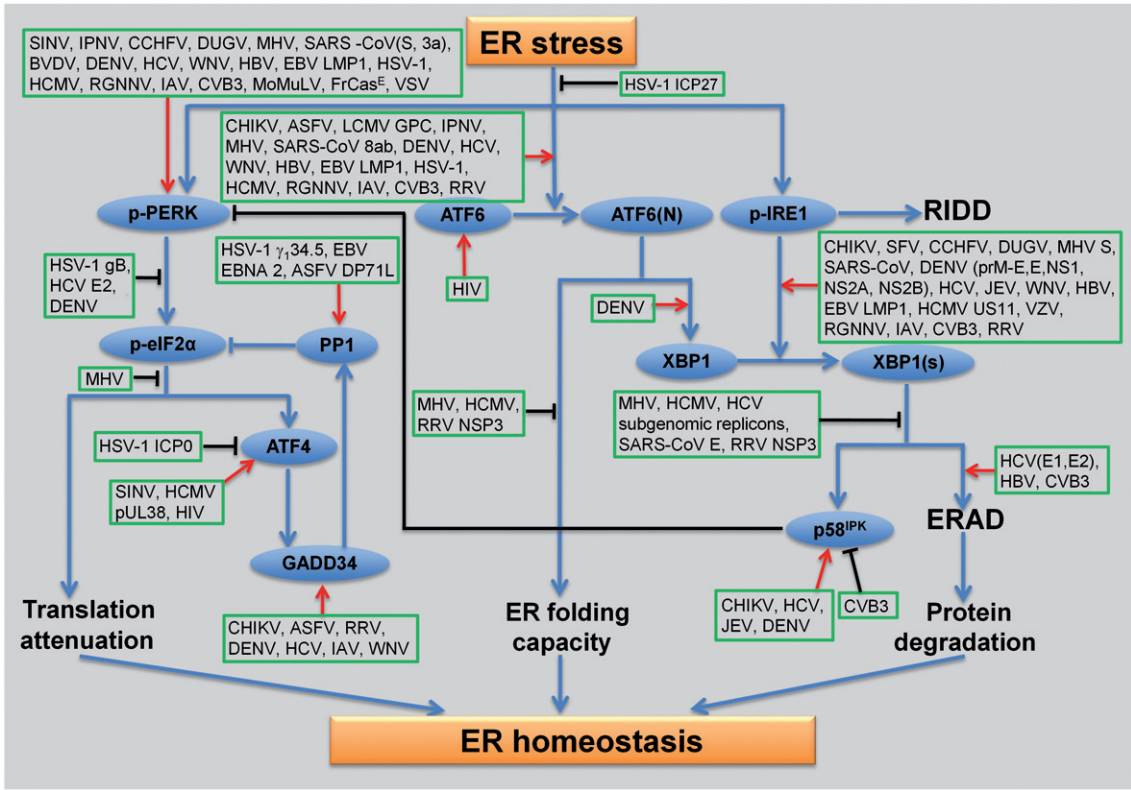

Figure 1. Modulation of the UPR by viruses. In virus-infected cells, three membrane transducers: PERK, ATF6, IRE1 are differentially activated to gain ER homeostasis. Arrows represent activation of the UPR components by virus infection; lines indicate inhibition of the UPR components by virus infection or inhibition between the UPR components.

their life cycles including virus entry, viral protein synthesis and modifications, genome replication and virus assembly (He, 2006; Inoue & Tsai, 2013). During productive viral infection, viruses hijack the host translation apparatus to produce a large amount of viral proteins accumulated in the ER lumen. Some viruses even utilize the ER as their replication sites such as Hepatitis C virus (HCV) (Moradpour et al., 2007) and African swine fever virus (ASFV) (Galindo et al., 2012). These activities of alien pathogens may disrupt the homeostasis of the ER and lead to a rapid accumulation of malfolded and unfolded proteins inside the ER lumen. Consequently, cells face great challenges and stress, so called ER stress, which may cause a wide variety of prevalent diseases such as neurodegenerative diseases, renal disease, liver disease and cancer (Hetz, 2012). To alleviate the detrimental effects of ER stress, cells evolved an ER-to-nucleus signaling pathway termed the unfolded protein response (UPR), which functions to restore the ER homeostasis (Bernales et al., 2006; Schroder & Kaufman, 2005). However, if under unsolved or intense ER stress, cells would fail to regain the ER homeostasis and instead, initiate the intrinsic apoptotic cascades, which have been thought to primarily associate with virus pathogenesis (Galluzzi et al., 2008). Here, we give a comprehensive description about the dynamic relationship between ER stress and virus infection with emphasis on how UPR and apoptosis influence viral replication and pathogenesis as well as the strategies employed by viruses to cope with ER stress. In particular, we discuss the current developed ER stress-related antivirals including broad-spectrum therapy by targeting ER stress signaling pathways and specifically targeted antiviral therapy by disturbing the functions of ER stress-triggering viral proteins.

Virus, ER stress and the UPR

Overview of ER stress-mediated UPR

In mammalian cells, the ER stress is sensed and mediated by three ER transmembrane receptors: pancreatic ER kinase (PKR)-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6). In resting cells, these three sensors are maintained in inactive states through interactions with the ER resident chaperone glucose regulated protein 78 (GRP78); while when unfolded or misfolded proteins accumulate in the ER lumen, GRP78 dissociates from these three transducers, resulting in their activation and initiation of the UPR (Figure 1).

PERK-eIF2α pathway

PERK is a type I ER-resident transmembrane kinase (Bernales et al., 2006; Lin et al., 2008). When it senses ER stress, PERK undergoes oligomerization and autophosphorylation to form active PERK, which then phosphorylates the α subunit of the eukaryotic translation initiation factor-2 (eIF2α) to reduce global protein synthesis and thus relieve the ER stress (Harding et al., 2000). However, this limited amount of active eIF2α selectively increases the translation of activating transcription factor-4 (ATF4), a pro-survival transcription factor that facilitates cell survival through activating

genes involved in amino acids biosynthesis and transport, stress response, redox reactions and protein secretion (Harding et al., 2000). One target gene of ATF4 is growth arrest and DNA damage-inducible 34 (GADD34), a protein phosphatase 1 (PP1) regulatory subunit that recruits PP1 to dephosphorylate eIF2α and derepresses PERK-eIF2α-mediated translation attenuation, thereby constituting a negative feedback loop in the UPR (Novoa et al., 2001).

IRE1-XBP1 pathway

The IRE1-XBP1 pathway is a highly conserved UPR branch in eukaryotic cells, which starts with activation of IRE1, a dual-activity enzyme harboring a serine-threoine kinase domain and an endoribonuclease domain (Sidrauski & Walter, 1997; Szegezdi et al., 2006). When IRE1 dissociates from GRP78, it undergoes oligomerization, which in turn activates its kinase and endonuclease activities. Activated IRE1 removes a 26-nucleotide intron from X box-binding protein 1 (XBP1) mRNA to form a spliced XBP1 (XBP1(s)), which is subsequently translated into a basic-zipper (bZIP) transcription factor that activates the transcription of genes that enhance the ER protein-folding capacity, phospholipid biosynthesis and ER-associated protein degradation (ERAD) (Lee et al., 2003; Shaffer et al., 2004). XBP1(s) is also able to activate the HSP40 family member $P58^{IPK}$, which can bind PERK and inhibit its activity to phoshporylate eIF2α (Yan et al., 2002). IRE1, by itself, can degrade ER-bound mRNAs through the regulated IRE1-dependent decay (RIDD) pathway to reduce protein translation and limit unfolded protein load in the ER lumen (Hollien et al., 2009).

ATF6 pathway

ATF6 is a bZIP transcription factor but is initially synthesized as a type II transmembrane protein having an ER stress-sensing luminal domain, transmembrane domain and a cytosolic N-terminal domain (Walter & Ron, 2011). In response to ER stress, ATF6 is packaged in ER-derived transport vesicles and translocates into the Golgi complex, where two specific proteases cleave its transmembrane domain and liberate its active N-terminal DNA binding domain, ATF6 (N) (Ye et al., 2000). ATF6 (N) then translocates into the nucleus and activates genes that improve the ER folding capacity such as ER chaperones, protein disulphide isomerase (PDI) as well as XBP1 (Yoshida et al., 2001). Overall, these three branches function to remedy ER stress by reducing the flux of newly synthesized polypeptides into the ER, degrading ER-localized proteins and expanding the ER folding capacity.

Induction of ER stress and UPR by virus infection

Emerging evidence indicates that a large number of viruses are capable of eliciting ER stress during their infection, which is summarized in Table 1. Currently, 35 animal and 1 plant viruses, which belong to 18 virus families with the majority being RNA viruses, have been reported to trigger ER stress indicators including inducing ER chaperones and activating three UPR sensors. 19 viruses have been reported to induce the expression of ER chaperone proteins (Bip, GRP78, GRP94, calnexin, calreticulin), which might be caused by accumulation of malfolded and unfolded viral proteins inside the ER lumen. These viruses include Potato virus X (PVX), Chikungunya virus (CHIKV), ASFV, Infectious pancreatic necrosis virus (IPNV), Tula virus (TULV), Porcine epidemic diarrhea virus (PEDV), Bovine viral diarrhea virus (BVDV), Dengue virus (DENV), Japanese encephalitis virus (JEV), Hepatitis B virus (HBV), Hepatitis E virus (HEV), Herpes simplex virus type 1 (HSV-1), Canine distemper virus (CDV), Human respiratory syncytial virus (RSV), Simian virus 5 (SV5), Coxsackievirus B3 (CVB3), Human immunodeficiency virus (HIV), Moloney murine leukemia virus-TB (MoMuLV), and Neurovirulent mouse retrovirus ($FrCas^E$) (Table 1). Intriguingly, upon virus-triggered ER stress, the three UPR transmembrane sensors are differentially activated: 19, 17 and 14 viruses have been reported to activate the PERK-eIF2α, IRE1-XBP1 and ATF6 branches, respectively (Table 1 and Figure 1), implying that cells prefer to initiate the PERK-eIF2α pathway in response to virus infection, presumably because the PERK-eIF2α-mediated global translational attenuation can efficiently restrict virus replication by preventing the synthesis of viral and cellular proteins crucial for virus life cycle (Baltzis et al., 2004; Pena & Harris, 2011). Nonetheless, it should be noted that at least two other eIF2α kinases, double-stranded RNA-dependent protein kinase (PKR) and general control non-derepressible-2 (GCN2) could be activated upon virus infection to restrict virus replication by preventing protein translation (Berlanga et al., 2006; Garcia et al., 2007). Hence, the role of PERK in translational attenuation could change depending on the virus.

Characteristics of ER stress-triggering viruses and viral proteins

Four pieces of information could be inferred from these published data about the characteristics of ER stress-triggering viruses and viral proteins, which could be useful in predicting the outcome of virus infection and unveiling the underlying pathogenic mechanisms. First, ER stress-triggering viruses are usually those have cytopathogenic or virulence effects. For the same type of viruses, the avirulent strain triggers no or mild ER stress such as the nonvirulent mouse retrovirus F43 (Dimcheff et al., 2004), noncytopathic mild Dugbe virus (DUGV) (Rodrigues et al., 2012), and the attenuated HSV-1 strain KOS (Mao et al., 2001), suggesting that ER stress is associated with viral virulence and pathogenesis. One exception is Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) lacking the envelope (E) gene, which is attenuated *in vivo* but elicits higher UPR than SARS-CoV with E gene (DeDiego et al., 2011). Second, the ER-tropic viruses that exploit the host ER as an integral part of their life cycle are prone to trigger ER stress, such as *Flaviviridae* viruses (HCV, BVDV and JEV), *Asfarviridae* virus ASFV, and *Coronaviridae* viruses, which use the ER as the primary site of glycoprotein biosynthesis, genome replication and even particle assembly (de Haan & Rottier, 2005; Galindo et al., 2012; Knoops et al., 2008; Leyssen et al., 2000; Oostra et al., 2007). Third, viruses that modify the ER in order to create a compartment suitable for virus replication are also inclined to induce the ER stress. For example, DENV,

Table 1. Interconnection between of ER stress and virus infection.

Virus	Impact of virus infection on ER stress: UPR (life)	Impact of virus infection on ER stress: Apoptosis (death)*	Impact of ER stress on virus replication and pathogenesis	References
Alphaflexiviridae (RNA)				
PVX	Induces BiP, PDI, calreticulin, and calmodulin Viral proteins: PVX TGBp3	Unknown	UPR alleviates ER stress-related apoptosis.	Ye et al., 2011
Alphavirus (RNA)				
CHIKV	Induces Bip, Hsp90, GADD34 and $p58^{IPK}$, activates ATF6 and IRE1-XBP1, suppresses eIF2α phosphorylation Viral proteins: CHIKV nsP4	Unknown	Unknown	Rathore et al., 2013
SFV	Activates IRE1-XBP1 Viral proteins: SFV envelope glycoproteins	Leads to loss of MMP†, cytochrome *c* release and activation of CHOP, caspase-3, -8, -9 and -12	Activated IRE1-XBP1 branch could promote SFV-induced apoptosis.	Barry et al., 2010; Urban et al., 2008
SINV	Activates IRE1-XBP1 and PERK, induces translation of ATF4	Induces CHOP, activates apoptosis	Activated UPR limits SINV replication.	Nivitchanyong et al., 2009; Perry et al., 2012; Rathore et al., 2013
Arenavirus (RNA)				
LCMV	Activates ATF6. Viral proteins: LCMV glycoprotein precursor (GPC)	Unknown	Activated ATF6 branch promotes virus replication and cell viability.	Pasqual et al., 2011
Asfarviridae (DNA)				
ASFV	Induces calnexin and calreticulin, activates ATF6 and GADD34	Activates caspase-3, -9 and -12, inhibits CHOP	Activated ATF6 pathway facilitates virus replication. The early activation of caspase-3 is required for virus exit.	Andrés et al., 1998; Galindo et al., 2012; Netherton et al., 2004
Birnaviridae (RNA)				
IPNV	Induces GRP78, activates ATF6 and PERK-eIF2α	Induces PERK-mediated CHOP transcription, MMP loss and activates caspase-3 and -8 Viral protein: IPNV VP5.	ER stress leads to IPNV-infected cell death.	Hong et al., 2002; Hong et al., 2005; Huang et al., 2011
Bunyaviridae (RNA)				
CCHFV	Activates IRE1-XBP1 and PERK	Induces PUMA, Noxa, CHOP and Bax	Activated ER stress and apoptosis contributes to virus pathogenesis.	Rodrigues et al., 2012
DUGV	Induces XBP1 and PERK	Induces no apoptosis	Unknown	Rodrigues et al., 2012
TULV	Induces GRP78 transcription Viral proteins: TULV glycoproteins	Induces CHOP and JNK pathways, activates caspase-12, -8 and -3	ER stress leads to TULV-infected cell death.	Li et al., 2005
Coronavirus (RNA)				
MHV	Modulates three UPR branches Viral protein: MHV spike (S) protein	Unknown	MHV modulates the UPR to facilitate its replication.	Bechill et al., 2008; Versteeg et al., 2007
IBV	Unknown	Induces CHOP/GADD153 and Bak, activates Mcl-1	Apoptosis facilitates virus release.	Zhong et al., 2012
PEDV	Induces GRP78 Viral protein: PEDV E and N	Induces Bcl-2 Viral protein: PEDV E	PEDV E might protect cells from apoptosis.	Xu et al., 2013a; Xu et al., 2013b
SARS	Activates PERK-eIF2α and IRE1-XBP1 Viral proteins: SARS S, 3a, 8ab and E	Induces apoptosis Viral protein: SARS-CoV E	SARS-CoV E reduces apoptosis, which might limit virus production and dissemination.	Chan et al., 2006; DeDiego et al., 2011; Minakshi et al., 2009; Sung et al., 2009

(*continued*)

Table 1. Continued

Virus	Impact of virus infection on ER stress: UPR (life)	Impact of virus infection on ER stress: Apoptosis (death)*	Impact of ER stress on virus replication and pathogenesis	References
Flaviviridae (RNA)				
BVDV	Induces GRP78, activates PERK-eIF2α	Induces CHOP, represses Bcl-2, activates caspase-12 Viral proteins: envelope glycoproteins	ER stress leads to BVDV-infected cell death.	Jordan et al., 2002; Schweizer & Peterhans, 1999
DENV	Activates PERK-eIF2α, ATF6 and IRE1-XBP1, induces GADD34 Viral proteins: DENV glycoproteins prM-E, E, NS1, NS2A, and NS2B	Damages MMP	The active XBP1(s) might be responsible for DENV-induced ER expansion. The PERK and IRE1-XBP1 pathways inhibit DENV replication. GRP78 facilitates virus replication.	Edgil et al., 2006; Limjindaporn et al., 2009; Pena & Harris, 2011; Umareddy et al., 2007; Yu et al., 2006
HCV	Activates three UPR branches. HCV sub-genomic replicons repress XBP1(s). Viral proteins: HCV E1, E2, NS2, NS4B, NS5A and core	Activates PERK-eIF2α-ATF4-CHOP pathway Viral proteins: HCV E1, E2 and core	Unknown	Benali-Furet et al., 2005; Bureau et al., 2001; Chan & Egan, 2005; Joyce et al., 2009; Li et al., 2009; Merquiol et al., 2011; Tardif et al., 2004; von dem Bussche et al., 2010
JEV	Induces calnexin, PDI, GRP78 and GRP94, activates IRE1-XBP1 Viral proteins: JEV glycoproteins prM, E, NS1, NS2A, NS2B and NS4B	Induces CHOP and ER stress-mediated cell apoptosis	GRP78 promotes mature viral production and subsequent cellular infections. The active XBP1(s) might be responsible for JEV-induced ER expansion.	Su et al., 2002; Wu et al., 2011; Yu et al., 2006
WNV	Activates XBP1 splicing, ATF6 proteolysis and eIF2α phosphorylation Viral proteins: nonstructural proteins	Induces GADD34 and CHOP, activates caspase-3 Viral proteins: WNV nonstructural proteins	CHOP-dependent apoptosis limits viral replication.	Ambrose & Mackenzie, 2011; Medigeshi et al., 2007
Hepadnaviridae (DNA)				
HBV	Induces GRP94, activates three UPR arms and ERAD pathway Viral proteins: HBx, S, and SHBs	Activates caspase-3 and -9 Viral protein: HBx	The ERAD pathway reduces the amount of virus envelope proteins to control the level of virus particles and facilitates chronic infections. Apoptosis limits the spread of HBV progeny.	Arzberger et al., 2010; Kuo et al., 2012; Lazar et al., 2012; Li et al., 2007; Li et al., 2011
Hepeviridae (RNA)				
HEV	Interacts with Grp78, induces Hsp72, Hsp70B' and Hsp40. Viral protein: HEV ORF2	Activates PERK- eIF2α-ATF4-CHOP pathway, but has no effect on apoptosis Viral protein: HEV ORF2	HEV ORF2-mediated Hsp72, Hsp70B' and Hsp40 inhibits CHOP-mediated apoptosis.	John et al., 2011; Yu et al., 2011
Herpesviridae (DNA)				
EBV	Activates three UPR branches Viral protein: EBV LMP1	Unknown	ER stress mediates the transition of EBV from latency to lytic replication.	Bhende et al., 2007; Lee & Sugden, 2008a, 2008b; Sun & Thorley-Lawson, 2007; Taylor et al., 2011
HSV-1	Induces GRP78, activates ATF6 and PERK-eIF2α-ATF4 at different infection stages Viral proteins: HSV-1 ICP0, glycoprotein B, $\gamma_1$34.5 and Us11	Unknown	HSV $\gamma_1$34.5-mediated eIF2α dephosphorylation facilitates HSV replication.	Boyce et al., 2005; Burnett et al., 2012; Cheng et al., 2005; He et al., 1997; Mao et al., 2001; Mulvey et al., 2007; Mulvey et al., 2003
HCMV	Modulates three UPR branches Viral proteins: HCMV US2, US11, pUL37x1, and pUL38	Inhibits apoptosis Virus proteins: HCMV pUL38, UL36, and pUL37x1	Induced GRP78 facilitates virion assembly and egress.	Buchkovich et al., 2008; Hegde et al., 2006; Isler et al., 2005; Keay et al., 1995; Qian et al., 2011; Sharon-Friling et al., 2006; Skaletskaya et al., 2001; Tirosh et al., 2005; Xuan et al., 2009
VZV		Unknown		Carpenter et al., 2011

	Activates IRE1-XBP1, induces CHOP Viral proteins: VZV gE and gI		Activated XBP1(s) might lead to VZV-caused ER expansion.	
Nodaviridae (RNA)				
RGNNV	Activates three UPR branches	Activates caspase-12, inhibits PERK-mediated Bcl-2 Viral proteins: RGNNV α and B2	GRP78 facilitates virus replication at a middle replication stage.	Su et al., 2011; Wu et al., 2010
Orthomyxoviridae (RNA)				
IAV	Activates three UPR branches Viral proteins: IAV hemagglutinin A	Induces caspase-3, -8, -9, -12, CHOP and GADD34	Activated IRE1-XBP1 branch facilitates IAV replication.	Hassan et al., 2012; Roberson et al., 2012
Paramyxoviridae (RNA)				
CDV	Induces calnexin	Alters Ca^{2+} homeostasis, induces calnexin and CHOP Virus proteins: CDV glycoproteins (F and H)	CDV-induced apoptosis could eventually lead to the neurodegeneration.	Brunner et al., 2007, 2012
RSV	Induces GRP78 and calnexin	Activates caspase-3 and -12 RSV NS1 and NS2 suppress early apoptosis.	RSV NS1 and NS2 suppress early apoptosis to facilitate virus replication. The RSV-induced apoptosis is a major cause of destruction of the lung epithelial in RSV-infected patients.	Bitko & Barik, 2001; Bitko et al., 2007
SV5	Induces GRP78, GRP94 and CHOP Viral protein: SV5 HN glycoprotein and V	Inhibits apoptosis Virus proteins: SV5 SH and V	Unknown	Sun et al., 2004; Watowich et al., 1991
Picornaviridae (RNA)				
CVB3	Induces GRP78, activates three UPR branches and ERAD, down-regulates $p58^{IPK}$	Induces CHOP-mediated apoptosis	ER stress mediates CVB3-induced apoptosis.	Zhang et al., 2010
Reoviridae (RNA)				
RRV	Modulates IRE1- XBP1 and ATF6 Viral proteins: RRV NSP3	Induces apoptosis, activates CHOP expression	Unknown	Martin-Latil et al., 2007; Trujillo-Alonso et al., 2011
Retrovirus (RNA)				
HIV	Activates ATF6 and ATF4, induces Bip	Triggers cytochrome *c* release, activates caspase-8, -9 and -3	Up-regulated ATF4 enhances HIV replication	Caselli et al., 2012; Lindl et al., 2007; Nie et al., 2002
MoMuLV	Activates PERK-eIF2α, induces GRP78 and CHOP Viral protein: MoMuLV $gPr80^{env}$	Leads to altered Ca^{2+} homeostasis, MMP dissipation, activation of caspase-3, -9, and -12	ER stress mediates MoMuLV-induced apoptosis.	Kim et al., 2004; Liu et al., 2004
$FrCas^{E}$	Induces GRP78, CHOP, calretrclin and PERK Viral proteins: $FrCas^{E}$ envelope protein $pr85^{env}$	Unknown	Unknown	Dimcheff et al., 2003
Rhabdoviridae (RNA)				
VSV	Activates PERK-eIF2α Viral protein: VSV G	Activates caspase-12, caspase-8 and -9 Viral protein: VSV M	Activated PERK pathway inhibits VSV replication.	Baltzis et al., 2004; Gaddy and Lyles, 2005; Machamer et al., 1990

*only viruses that affect intrinsic mitochondrial apoptosis have been listed;
†MMP, mitochondrial membrane potential.

VZV and JEV have been shown to stimulate ER proliferation and HCV has been reported to alter the ER structure (Carpenter et al., 2011; Hase et al., 1992; Moradpour et al., 2007; Umareddy et al., 2007; Yu et al., 2006). Fourth, the viral proteins that are synthesized, processed or located in the ER tend to trigger the ER stress, including PXV TGBp3, PEDV (E, N), the glycoproteins of viruses (SFV, LCMV, TULV, BVDV, DENV, JEV, VZV, SV5, HSV-1 and VSV) and ER-membrane-anchored or transmembrane proteins (SARS-CoV (3a, 8ab), HCV (NS4B, E2)) (Table 1). Although the precise mechanism remains elusive for most viral proteins, certain viral proteins could trigger ER stress via their interactions with ER chaperone GRP78 such as HCV E2 (Choukhi et al., 1998), VSV G (Machamer et al., 1990), DENV E (Limjindaporn et al., 2009), and SV5 hemagglutinin-neuraminidase (HN) glycoprotein protein (Watowich et al., 1991).

Predicted ER stress-triggering viruses and viral proteins

As viruses that modify or alter the ER tend to induce ER stress, we predict the following viruses might trigger ER stress and activate related signaling pathways. The *Picornaviridae* family virus Poliovirus, *Poxviridae* DNA virus vaccinia virus (VV), *Comoviridae* family virus Grapevine fanleaf nepovirus (GFLV) and *Bromoviridae* family virus Brome mosaic virus (BMV) as their infection can cause extensive cytopathic modifications to host ER and/or induce ER-derived virus vesicles (Bamunusinghe et al., 2011; Ritzenthaler et al., 2002; Suhy et al., 2000; Tolonen et al., 2001). Since viral proteins that are synthesized, processed or located in the ER tend to induce the ER stress, Yellow fever virus (YFV) envelope proteins, pre-membrane (prM) and envelope (E), might trigger the ER stress as these proteins accumulate in the ER (Ciczora et al., 2010). Based on the fact that some viral proteins can trigger ER stress through interacting with ER chaperones, the *Togaviridae* family virus Rubella virus (RV) glycoproteins E1 and E2 might trigger ER stress as these two proteins interact with ER chaperones calreticulin and calnexin (Nakhasi et al., 2001). Moreover, our assumptions could provide possible activating mechanisms for those experimentally validated ER stress-triggering viruses. For example, as the ER stress-triggering virus, CVB3 has been reported to modify the ER membrane permeability (van Kuppeveld et al., 1997), it is highly likely that this activity could be responsible for CVB3-induced ER stress. Given the facts that certain viral proteins trigger ER stress via their interactions with ER chaperone GRP78 and that the ER stress inducer, HEV ORF2 has been shown to interact with GRP78 (Yu et al., 2011), it is possible that this interaction could activate ER stress. Further efforts are required to examine these possibilities.

Modulation of the UPR by viruses

The UPR has three major consequences to mitigate ER stress: attenuating global protein translation, degrading ER-localized proteins and expanding the ER folding capacity, some of which are beneficial to viral replication. For example, the ATF6-induced expression of chaperone proteins may help viral proteins folding and prevent protein aggregation. The PERK-eIF2α-activated ATF4 may help re-establish cell metabolism and resume protein translation. The IRE1-XBP1 pathway might facilitate virus replication by enhancing ER protein-folding ability and ER membrane biosynthesis (Ron & Hampton, 2004). In fact, activated ATF6 has been reported to promote the replication of ASFV (Galindo et al., 2012) and Lymphocytic choromeningitis virus (LCMV) (Pasqual et al., 2011); GRP78 facilitates the replication of DENV (Limjindaporn et al., 2009), HCMV (Buchkovich et al., 2008), JEV (Wu et al., 2011) and RGNNV (Su et al., 2011; Wu et al., 2010) and activated ATF4 facilitates HIV replication (Caselli et al., 2012). The IRE1-XBP1 pathway has been activated by IAV to facilitate its own replication (Hassan et al., 2012). However, other UPR outcomes are detrimental for virus replication. The PERK-eIF2α-mediated global translation attenuation is known as an antiviral response to restrict the replication of WNV (Ambrose & Mackenzie, 2011), DENV (Pena & Harris, 2011) and VSV (Baltzis et al., 2004). The IRE1-XBP1(s)-mediated ERAD pathway reduces intracellular HBV particles by degrading its envelope proteins (Lazar et al., 2012). In addition, the IRE1-XBP1 pathway inhibits the replication of Sindbis virus (SINV) and DENV through an unknown mechanism (Pena & Harris, 2011; Perry et al., 2012). To survive and propagate in host cells, viruses have evolved specific mechanisms to modulate the UPR (Figure 1).

Subversion of the UPR by viruses

Although the PERK-eIF2α pathway reduces global protein synthesis, some viruses are still able to translate their mRNAs regardless of high levels of phosphorylated eIF2α, such as HCV (Robert et al., 2006) and SFV (Ventoso et al., 2006). These viruses contain a specialized internal ribosome entry site (IRES) that can efficiently recruit and assemble the initiation ribosome complex (Robert et al., 2006; Ventoso et al., 2006). Besides, some viruses have developed additional ''smart'' strategies to circumvent PERK-eIF2α-mediated inhibitory effects and reset the cellular translational program for their own purposes (Table 1 and Figure 1). One salient strategy is to reduce the phosphorylated eIF2α by activating eIF2α phosphatase PP1 and inducing its regulatory subunit GADD34. The HSV-1 $\gamma_1$34.5, Epstein-Barr virus (EBV) nuclear antigens (EBNA 2) and ASFV DP71L proteins are GADD34 homologs that interact with PP1 and recruit its activity against eIF2α (He, 2006; Rivera et al., 2007); while viruses like CHIKV, ASFV, RRV, DENV, HCV, Influenza A virus (IAV) and WNV activate the expression of GADD34 (Galindo et al., 2012; Hassan et al., 2012; Medigeshi et al., 2007; Merquiol et al., 2011; Pena & Harris, 2011; Rathore et al., 2013; Trujillo-Alonso et al., 2011). HCV and HIV might employ similar strategy to antagonize eIF2α phosphorylation as HCV NS4B protein has been predicted to interact with PP1 and PP1 is required for HIV replication (Ammosova et al., 2003; Li et al., 2012). Another strategy involves regulation of the PERK activity. HSV-1 glycoprotein B(gB) interacts with the PERK luminal domain, which makes it refractory to acute ER stress (Mulvey et al., 2007). The *Alphavirus* CHIKV and *Flaviviridae* viruses (HCV, JEV and

DENV) could repress the activity of PERK via transcriptional up-regulation of its inhibitor, $p58^{IPK}$ (Merquiol et al., 2011; Rathore et al., 2013; Yu et al., 2006). Some viral proteins even function as a pseudo-substrate of PERK to sequester its activity such as HCV E2 protein (Pavio et al., 2003) and DENV has been proposed to encode a viral protein similar to HCV E2 to block the PERK-mediated eIF2α phosphorylation (Pena & Harris, 2011).

The IRE1-XBP1 pathway is subject to modulation during the course of virus infection (Table 1 and Figure 1). HCV subgenomic replicons and HCMV infection suppress the IRE1-XBP1 pathway by inhibiting the transcriptional activity of XBP1(s) as well as transcriptional induction of EDEM presumably to enhance the synthesis of their viral proteins and persistent infection (Isler et al., 2005; Tardif et al., 2004). SARS-CoV E protein down-regulates the IRE1-mediated XBP1 splicing to reduce the ER stress (DeDiego et al., 2011). It remains to be elucidated whether viruses modulate the IRE1-mediated RIDD pathway.

Lastly, Rhesus rotavirus (RRV) NSP3 protein has been shown to impede the activation of two UPR branches, IRE1-XBP1 and ATF6, despite the fact that it induces XBP1 splicing and ATF6 proteolysis (Trujillo-Alonso et al., 2011). The three UPR branches are inhibited by MHV (Bechill et al., 2008) and HCMV (Isler et al., 2005). Although these two viruses induce XBP1 splicing, ATF6 proteolysis and PERK phosphorylation, they suppress the activation of their downstream targets. It is unclear about the specific mechanism by which these viruses regulate the UPR pathways as well as how viruses benefit from shutdown of these three UPR arms.

Temporal regulation of the UPR by viruses

Viruses also differentially modulate the UPR at different infection stages and the prominent example is DENV (Pena & Harris, 2011). Very early DENV infection induces PERK-mediated eIF2α phosphorylation but then suppresses that pathway. The IRE1-XBP1 and ATF6 pathways are activated during the mid and late infection, respectively, to help cells establish ER homeostasis and adapt to persistent ER stress without inducing apoptosis. HCV has also been shown to activate UPR in a temporal manner (Merquiol et al., 2011). There are two possible mechanisms that are responsible for the temporally modulated UPR by viruses. The first mechanism is related to differential expression of viral proteins at different stages and the typical example is HSV-1 (Burnett et al., 2012). During its early infection stage, only ATF6 proteolysis is induced but no up-regulation of its target chaperone proteins. Meanwhile, PERK-mediated eIF2α phosphorylation and ATF4 expression are down-regulated. These effects might be modulated by its early gene product ICP0. As virus infection proceeds, these activated UPR indicators are totally aborted due to its viral proteins, VHS and ICP27, which degrade certain cellular mRNAs (Elgadi et al., 1999). At the final infection stage, these inhibitory effects are relieved and cells initiate apoptosis, which may facilitate virus particles release from host cells. The second mechanism by which the UPR is temporally regulated is associated with the stability of viral proteins. For example, CHIKV suppresses phosphorylation of eIF2α at early infection stage due to expression of its nsP4 protein; however, as nsP4 protein is not stable, cells recovers phosphorylation of eIF2α at the late CHIKV infection stage (Rathore et al., 2013).

Virus, ER stress and apoptosis

Overview of ER stress-mediated apoptosis

Under acute or prolonged ER stress, cell apoptosis is activated marked by loss of mitochondrial membrane potential (MMP), release of cytochrome c from mitochondria into the cytosol and activation of caspases. Although little is known about how cells are committed to cell death, two ER stress sensors, IRE1 and PERK, are thought to mediate intrinsic mitochondrial apoptosis (Figure 2).

IRE1 apoptosis pathway

Under severe ER stress conditions, IRE1 exerts pro-apoptotic effects and functions as a critical factor controlling the commitment to cell death. The best-characterized mechanism is the IRE1-TRAF2-JNK pathway (Hotamisligil, 2010). Activated IRE1 interacts with the tumor necrosis factor receptor-associated factor-2 (TRAF2), which then recruits apoptosis-signal-regulating kinase (ASK1) to initiate a cascade of phosphorylation events that activates Jun amino-terminal kinase (JNK) (Urano et al., 2000). The pivotal mediators that link JNK to apoptosis are Bcl-2 family proteins, which include anti-apoptotic four Bcl-2 homology domain-containing (BH) proteins (Bcl-2, Bcl-X_L, Mcl-1), pro-apoptotic three BH-containing proteins (Bax, Bak) and pro-apoptotic BH3-only proteins (Bad, Bim, Bid, Noxa, Puma) (Galluzzi et al., 2008). BH3-only proteins are necessary for Bax/Bak-mediated mitochondrial permeabilization and release of Ca^{2+} from the ER into the cytosol but Bcl-2 promotes cell survival through sequestration of BH3-only proteins (Cheng et al., 2001). The released Ca^{2+} can be taken up by mitochondria, resulting in MPP loss and subsequent efflux of cytochrome c from mitochondria to cytosol, which ultimately leading to apoptosis. JNK phosphorylates Bcl-2 to reduce its anti-apoptotic activity but phosphorylates BH3-only proteins to enhance its pro-apoptotic effects (Szegezdi et al., 2006). Moreover, prolonged activation of IRE1-mediated RIDD pathway may cause apoptosis by degrading mRNAs encoding essential cell-survival proteins (Hollien et al., 2009).

PERK-eIF2α-ATF4-CHOP pathway

The activated PERK-eIF2α-ATF4 pathway promotes apoptosis by inducing the expression of CHOP (also called GADD153), which exerts pro-apoptotic effects by up-regulating the expression of pro-apoptotic proteins BH3-only protein and down-regulating anti-apoptotic protein Bcl-2 (Hetz, 2012). In addition, CHOP triggers apoptosis through inducing the transcription of death receptor-5 (DR5) (Yamaguchi & Wang, 2004), tribbles-related protein 3 (TRB3) (Ohoka et al., 2005), GADD34 and ER oxidase 1α (ERO1α) (Marciniak et al., 2004). DR5 is a critical mediator of ER stress-induced apoptosis in cancer cells and TRB3 promotes apoptosis presumably by binding to the pro-survival serine/threonine kinase Akt and reducing its kinase activity

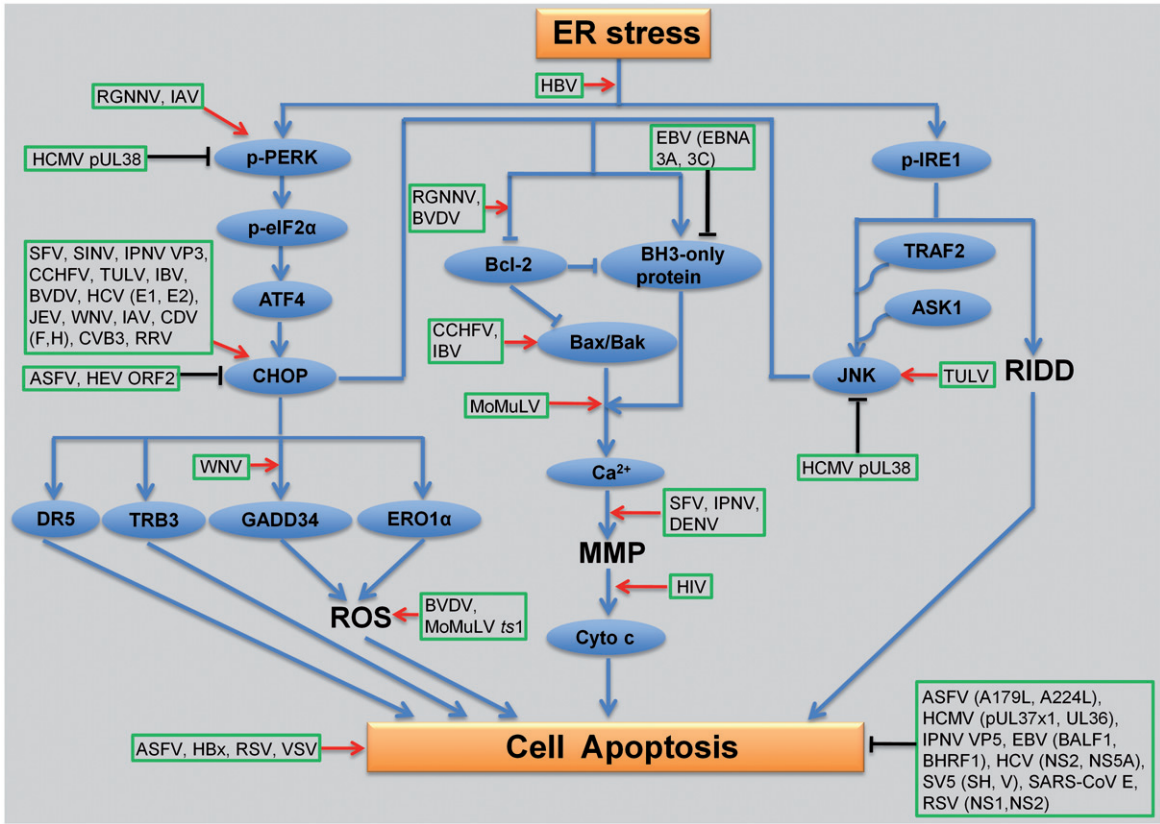

Figure 2. Modulation of apoptosis by viruses. Arrows indicate viruses and viral proteins that activate the components of apoptosis; lines indicate viruses and viral proteins that suppress the components of apoptosis; the left bottom box indicates the viruses that induce both ER stress and apoptosis but the causality between these two pathways is unknown; the right bottom box indicates the viruses that induce ER stress but repress apoptosis. HBV induces ER stress-mediated apoptosis but it is unknown which pathway contributes to apoptosis. Cyto c, cytochrome c.

(Yamaguchi & Wang, 2004). GADD34 and ERO1α mediate apoptosis by affecting the accumulation of reactive oxygen species (ROS) (Marciniak et al., 2004). The executioner of cell apoptosis by ER stress is a cohort of caspases including caspase-12, -3, -6, -7, -8 and -9 (Szegezdi et al., 2006).

Activation of apoptosis by ER stress-triggering viruses

Among 36 ER stress-triggering viruses, 23 viruses have been reported to induce or accelerate apoptosis, including Semliki Forest Virus (SFV), SINV, ASFV, IPNV, Crimean-Congo hemorrhagic fever virus (CCHFV), TULV, Infectious bronchitis virus (IBV), SARS-CoV, BVDV, DENV, HCV, JEV, West Nile virus (WNV), HBV, Betanodavirus redspotted grouper nervous necrosis virus (RGNNV), IAV, CDV, RSV, CVB3, Rhesus rotavirus (RRV), HIV, MoMuLV and Vesicular stomatitis virus (VSV) (Table 1 and Figure 2). This is not surprising given that their productive infection causes great damage to host cells. Among 23 apoptosis-inducing viruses, 5 viruses have been reported to trigger MMP loss and cytochrome c release into the cytosol including SFV, IPNV, DENV, HIV and MoMuLV. Four viruses (RGNNV, BVDV, CCHFV and IBV) might also induce MMP loss and cytochrome c release through regulating the upstream factors: Bcl-2, BH3-only proteins, Bax and Bak. 16 out of 23 viruses might induce apoptosis via the PERK-eIF2α-ATF4-CHOP pathway including SFV, SINV, IPNV, CCHFV, TULV, IBV, BVDV, HCV, JEV, WNV, RGNNV, IAV, CDV, CVB3, RRV and MoMuLV with WNV and HCV being shown to induce the expression of CHOP to promote apoptosis (Benali-Furet et al., 2005; Medigeshi et al., 2007). Although HEV infection activates the PERK-eIF2α-ATF4-CHOP pathway in human cells H1299, it fails to induce apoptosis (John et al., 2011). Only TULV activates the IRE1-TRAF2-JNK-dependent cell apoptosis. The rest four ER stress-triggering viruses (ASFV, HBV, RSV and VSV) are able to sensitize cells to apoptosis but it is unclear whether these effects are mediated by ER stress (Bitko & Barik, 2001; Gaddy & Lyles, 2005; Galindo et al., 2012; Kuo et al., 2012).

Modulation of apoptosis by ER stress-triggering viruses

The ER stress-mediated apoptosis plays pivotal roles in virus pathogenesis (Table 1). For example, CDV-induced apoptosis may eventually lead to the neurodegenerative disease (Brunner et al., 2012). The RSV-induced cell death is a major cause of destruction of the lung epithelial in RSV-infected patients (Bitko & Barik, 2001). Apoptosis is also required for virus replication such as release and dissemination of virus particles. Activation of caspase-3 at the early stage of ASFV infection is required for virus exit (Galindo et al., 2012). Knockdown Mcl-1 in IBV-infected mammalian cells accelerates apoptosis and increases IBV progeny production and release, while knockdown Bak delays apoptosis and reduces the release of viral proteins and particles

(Zhong et al., 2012). However, premature cell apoptosis may function as a host defense response by limiting virus replication and pathogenesis. For example, the virus titers of WNV are significantly increased in CHOP-deficient cells that are resistant to ER stress-mediated apoptosis (Medigeshi et al., 2007). In addition, HBV has been shown to prevent apoptosis to facilitate the release and spread of infectious progeny (Arzberger et al., 2010).

To overcome the host resistance, viruses have evolved a battery of distinct strategies to subvert apoptosis to optimize their infection (Table 1 and Figure 2). One strategy is to modulate the expression and/or activity of components in the apoptotic pathways including the PERK-eIF2α-ATF4-CHOP and IRE1-TRAF2-JNK. HCMV pUL38 protein has been reported to protect primary human foreskin fibroblasts from apoptosis by blocking the phosphorylation of PERK and activation of JNK (Xuan et al., 2009). ASFV infection down-regulates the transcription of CHOP, perhaps to prevent host cell death and prolong viral replication (Galindo et al., 2012; Galluzzi et al., 2008). Some viruses modulate apoptosis by targeting BH3-only proteins and Bcl-2 protein. EBV EBNA 3A and 3C proteins suppress the expression of BH3-only protein Bim and Noxa in B cells (Yee et al., 2011). PEDV E protein might suppress apoptosis by up-regulating anti-apoptotic Bcl-2 (Xu et al., 2013a) and further efforts are required to confirm it. Certain ER stress-triggering viruses inhibit apoptosis by modulating the activities of caspases. For example, ASFV A224L protein inhibits caspase-3 (Galluzzi et al., 2008) and HCMV UL36 protein blocks apoptosis by binding to the pro-domain of caspase-8 and inhibiting its activation (Skaletskaya et al., 2001). Other strategy involves encoding anti-apoptotic viral proteins that share significant sequence similarity with Bcl-2 family and these viral Bcl-2 proteins (vBcl-2s) preferentially bind to pro-apoptotic Bax and Bad and inhibit Bax/Bad-mediated apoptosis. For instance, IPNV VP5, ASFV A179L, HCMV pUL37x1 and EBV (BALF1, BHRF1) proteins exert anti-apoptotic effects presumably due to their Bcl-2 motif (Galluzzi et al., 2008; Hong et al., 2002). In addition, some viruses antagonize apoptosis by inducing the expression of chaperones or heat shock proteins, which could interfere with the functions of CHOP (Gotoh et al., 2004). HEV ORF2 protein has been suggested to prevent CHOP-mediated apoptosis through inducing Hsp70B', Hsp72 and Hsp40 (John et al., 2011). Besides, HCV (NS2, NS5A), SV5 (V, SH), SARS-CoV E and RSV (NS1, NS2) proteins have been reported to inhibit apoptosis through unknown mechanisms (Bitko & Barik, 2001; Bitko et al., 2007; DeDiego et al., 2011; Galluzzi et al., 2008; Sun et al., 2004).

Why do viruses have distinct effects on the UPR and apoptosis?

There are two possible explanations with regards to the nature of viruses and the type of cells they infected. First, compared with DNA viruses, RNA viruses usually have relatively short replication period and can replicate to high titers before the infected cells undergo cell death. Hence, most ER stress-triggering RNA viruses (SFV, IPNV, CCHFV, TULV, SARS-CoV, DENV, JEV, WNV, RGNNV, IAV, CDV, RSV, MoMuLV and $FrCas^E$) tend to induce apoptosis; while ER stress-triggering DNA viruses (ASFV, EBV, HCMV) tend to protect the infected cells from apoptosis (Table 1 and Figure 2). Second, various types of cells adapt the ER capacity for different purposes and accordingly, may respond differentially to exogenous stimuli. For example, compared with epithelial cells, hepatocytes are specialized secretory cells that synthesize and secret large quantities of proteins and thereby are more sensitive to ER stress (Hassan et al., 2012; Hetz, 2012). As expected, in HCV- or HBV-infected hepatocytes, the ATF6 pathway is preferentially activated to induce the transcription of chaperones; whereas in IAV-infected epithelial cells, ATF6 and its target chaperones are not activated (Hassan et al., 2012).

Virus, ER stress and immune responses

A growing body of evidence indicates that ER stress contributes to virus pathogenesis by modulating the immune responses in addition to causing apoptosis. VSV, HCV and SARS-CoV are able to inhibit the type I IFN signaling pathway by activating the PERK, which leads to the phosphorylation-dependent ubiquitination and subsequent degradation of the IFN α-receptor subunit 1 (IFNAR1), thereby promoting immune evasion and virus pathogenesis (Liu et al., 2009; Minakshi et al., 2009). WNV has also been reported to induce ER stress and inhibit type I IFN signaling pathway to facilitate the escape from the host immune response and viral pathogenesis (Ambrose & Mackenzie, 2011). HCMV US11 protein activates the UPR to facilitate the degradation of class I major histocompatibility complex, leading to immune evasion (Tirosh et al., 2005). Moreover, ER stress is responsible for viral pathogenesis by interconnecting with the inflammatory responses. For example, HCV induces inflammatory responses by activating IRE1, which interacts with TRAF2 to phosphorylate JNK, leading to activation of inflammation mediators (Merquiol et al., 2011; Zhang & Kaufman, 2008). HCV NS4B and NS5A activate NF-κB via ER stress-elicited calcium depletion and ROS production (Gong et al., 2001; Li et al., 2009). Cho et al. found that HBV X protein (HBx) induces the expression of COS2 (cyclo-oxygenase 2), a key mediator of inflammation, through PERK-eIF2α-activated ATF4 (Cho et al., 2011).

Implications for antiviral therapy

Since the ER stress plays expanding roles in virus replication and pathogenesis, the ER stress mediated signaling pathways have become attractive targets for broad-spectrum antiviral therapy and considerable progress has been made in developing potential antiviral agents. The first class of antiviral targets involves the three UPR pathways. The PERK-eIF2α pathway has been extensively investigated for antiviral development. Boyce and colleagues identified a small chemical compound salubrinal, a specific inhibitor of PP1/GADD34 complex and found it blocks HSV $\gamma_1$34.5-mediated eIF2α dephosphorylation and efficiently reduces HSV replication (Boyce et al., 2005). Salubrinal has also been shown to inhibit the replication of DENV through attenuating PP1/GADD34-mediated eIF2α dephosphorylation (Umareddy et al., 2007). The clinically achievable reagent

glucose analog 2-Deoxy-D-Glucose, which induces the phosphorylation of eIF2α, has been reported to suppress herpesvirus (KSHV) replication and serve as a novel anti-herpesviral therapy (Leung et al., 2012). Moreover, the IRE1-XBP1 pathway has become the target for antiviral development. Hassan et al. found that 3,5-dibromosalicyladehyde, which is a specific inhibitor of IRE1 endoribonuclease, significantly blocks IAV replication (Hassan et al., 2012). The IRE1-XBP1 pathway agonist, WP1130, has broad antiviral effects against SINV, murine norovirus (MNV-1) and La Crosse virus (Perry et al., 2012). It remains to be determined whether ATF6 and its downstream genes (chaperone proteins) can be potential targets. It is noteworthy that the selection of the UPR antagonists or agonists depends on the positive or negative effects of the UPR on virus replication.

Other targets involve ER stress-mediated intrinsic apoptosis signaling pathways. Rana catesbeiana ribonuclease (RC-RNase) has been shown to inhibit JEV replication through activating caspase-3, -8 and -9 (Lee et al., 2011). Rider et al. developed a broad-spectrum antiviral therapy, dubbed Double-stranded RNA activated caspase oligomerizer (DRACO) that selectively induces apoptosis in double-stranded virus infected cells but has no harmful effects on uninfected cells and this DRACO has successfully been shown to eliminate 15 different viruses including DENV and HIV (Rider et al., 2011). Besides, Vaticanol B has been well-studied as an effective agent that protects against ER stress-induced apoptosis (Tabata et al., 2007). In addition, the components of apoptotic pathway, Bcl-2 families, JNK and CHOP have been investigated in pre-clinical trials (Tabas & Ron, 2011).

The ER stress-triggering viral proteins could become targets for specifically targeted antiviral therapy, such as CHIKV nsP4, SFV envelope glycoproteins, LCMV glycoprotein precursor (GPC), TULV glycoproteins, IPNV VP3, MHV S, SV5 HN, PEDV (E and N), SARS-CoV proteins (S, 3a, 8ab, E), BVDV envelope glycoproteins, DENV proteins (prM-E, E, NS1, NS2A, NS2B), HCV proteins (E1, E2, core, NS2, NS4B, NS5A), JEV (prM, E, NS1, NS2A, NS2B, NS4B), WNV nonstructural proteins, HSV-1 (ICP0, glycoprotein B, $\gamma_1$34.5, Us11), HCMV (US2, US11, pUL37x1, UL36, pUL38), VZV (gE, gI), RGNNV (α and B2), IAV hemagglutinin A, CDV (F, H), SV5 (V, SH), RRV NSP3, MpMuLV gPr80^{env} and VSV M protein (Table 1). Special attention should be given to those viral proteins that can induce both the UPR and apoptosis signaling pathways such as HCV (E1, E2, core), HCMV (pUL37x1, pUL38) and SV5 V protein. Indeed, significant advances have been made in developing antivirals or vaccines against viral proteins: clemizol for HCV NS4B (Einav et al., 2010), vaccine vectors for HSV-1 $\gamma_1$34.5 (Shah et al., 2009), and Norakin for IAV hemagglutinin A (Ghendon et al., 1986).

Conclusions and perspectives

As a virus replication site and factory to process viral proteins, the ER is required for virus replication and suffers greatly from these alien pathogen activities. Current research indicated that 36 viruses trigger ER stress and related signal pathways during their activities. These ER stress responses play important roles in virus-induced apoptosis, immune evasion and inflammation, which have profound but complex implications in virus replication and pathogenesis. To combat with the deleterious effects of ER stress, viruses have developed elegant strategies to tune the ER stress-related pathways and these strategies differ dependent on the types of cells and viruses.

For the future directions, it is worth examining whether those predicted ER stress-triggering viruses can induce ER stress and modulate related signaling pathways. In addition, there are five open questions need to be addressed for future research. Firstly, for most ER stress-triggering viruses, less is known about the precise mechanism by which virus activates ER stress as much work is focused on detecting ER stress indicators during virus infection. Based on the published data (Table 1), the mechanisms may be related to the rapid synthesis and accumulation of viral proteins inside the ER lumen, the interactions of viral proteins with ER host factors including UPR sensors, the disturbance of ER membrane by virus replication. Secondly, for most ER stress-triggering viruses, it remains unclear about which viral protein(s) attributes to the occurrence of ER stress. Characterizing these proteins and elucidating the underlying mechanisms will undoubtedly help us understand the virus life cycle and pathogenesis. Most importantly, these viral proteins can be potential therapeutic targets to cure virus infection. Thirdly, little is known about how viruses activate the UPR transducers but selectively regulate their target genes. For example, ASFV activates ATF6 and its transcriptional targets calnexin and calreticulin but has no effects on XBP1 or GRP78 (Galindo et al., 2012). Fourthly, despite much is known about the regulation of ER stress by viruses, how virus-triggered ER stress regulates the intricate balance between pro-survival and pro-apoptotic effects and how these events results in cell death commitment remain enigmatic. Lastly, for most ER stress-triggering viruses, it remains to be determined to what extent virus-induced apoptosis can be explained by ER stress.

Declaration of interest

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References

Ambrose RL, Mackenzie JM. (2011). West Nile Virus differentially modulates the unfolded protein response to facilitate replication and immune evasion. J Virol 85:2723–32.

Ammosova T, Jerebtsova M, Beullens M, et al. (2003). Nuclear protein phosphatase-1 regulates HIV-1 transcription. J Biol Chem 278: 32189–94.

Andrés G, García-Escudero R, Simón-Mateo C, Viñuela E. (1998). African swine fever virus is enveloped by a two-membraned collapsed cisterna derived from the endoplasmic reticulum. J Virol 72: 8988–9001.

Arzberger S, Hosel M, Protzer U. (2010). Apoptosis of hepatitis B virus-infected hepatocytes prevents release of infectious virus. J Virol 84: 11994–2001.

Baltzis D, Qu LK, Papadopoulou S, et al. (2004). Resistance to vesicular stomatitis virus infection requires a functional cross talk between the

eukaryotic translation initiation factor 2alpha kinases PERK and PKR. J Virol 78:12747–61.
Bamunusinghe D, Seo JK, Rao AL. (2011). Subcellular localization and rearrangement of endoplasmic reticulum by Brome mosaic virus capsid protein. J Virol 85:2953–63.
Barry G, Fragkoudis R, Ferguson MC, et al. (2010). Semliki forest virus-induced endoplasmic reticulum stress accelerates apoptotic death of mammalian cells. J Virol 84:7369–77.
Bechill J, Chen Z, Brewer JW, Baker SC. (2008). Coronavirus infection modulates the unfolded protein response and mediates sustained translational repression. J Virol 82:4492–501.
Benali-Furet NL, Chami M, Houel L, et al. (2005). Hepatitis C virus core triggers apoptosis in liver cells by inducing ER stress and ER calcium depletion. Oncogene 24:4921–33.
Berlanga JJ, Ventoso I, Harding HP, et al. (2006). Antiviral effect of the mammalian translation initiation factor 2alpha kinase GCN2 against RNA viruses. EMBO J 25:1730–40.
Bernales S, Papa FR, Walter P. (2006). Intracellular signaling by the unfolded protein response. Annu Rev Cell Dev Biol 22:487–508.
Bhende PM, Dickerson SJ, Sun X, et al. (2007). X-box-binding protein 1 activates lytic Epstein-Barr virus gene expression in combination with protein kinase D. J Virol 81:7363–70.
Bitko V, Barik S. (2001). An endoplasmic reticulum-specific stress-activated caspase (caspase-12) is implicated in the apoptosis of A549 epithelial cells by respiratory syncytial virus. J Cell Biochem 80: 441–54.
Bitko V, Shulyayeva O, Mazumder B, et al. (2007). Nonstructural proteins of respiratory syncytial virus suppress premature apoptosis by an NF-kappaB-dependent, interferon-independent mechanism and facilitate virus growth. J Virol 81:1786–95.
Boyce M, Bryant KF, Jousse C, et al. (2005). A selective inhibitor of eIF2alpha dephosphorylation protects cells from ER stress. Science 307:935–9.
Brunner JM, Plattet P, Doucey MA, et al. (2012). Morbillivirus Glycoprotein Expression Induces ER Stress, Alters Ca Homeostasis and Results in the Release of Vasostatin. PLoS One 7:e32803.
Brunner JM, Plattet P, Majcherczyk P, et al. (2007). Canine distemper virus infection of primary hippocampal cells induces increase in extracellular glutamate and neurodegeneration. J Neurochem 103: 1184–95.
Buchkovich NJ, Maguire TG, Yu Y, et al. (2008). Human cytomegalovirus specifically controls the levels of the endoplasmic reticulum chaperone BiP/GRP78, which is required for virion assembly. J Virol 82:31–9.
Bureau C, Bernad J, Chaouche N, et al. (2001). Nonstructural 3 protein of hepatitis C virus triggers an oxidative burst in human monocytes via activation of NADPH oxidase. J Biol Chem 276:23077–83.
Burnett HF, Audas TE, Liang G, Lu RR. (2012). Herpes simplex virus-1 disarms the unfolded protein response in the early stages of infection. Cell Stress Chaperones 17:473–83.
Carpenter JE, Jackson W, Benetti L, Grose C. (2011). Autophagosome formation during Varicella-Zoster virus infection following endoplasmic reticulum stress and the unfolded protein response. J Virol 85: 9414–24.
Caselli E, Benedetti S, Gentili V, et al. (2012). Activating transcription factor 4 (ATF4) promotes HIV type 1 activation. AIDS Res Hum Retroviruses 28:907–12.
Chan CP, Siu KL, Chin KT, et al. (2006). Modulation of the unfolded protein response by the severe acute respiratory syndrome coronavirus spike protein. J Virol 80:9279–87.
Chan SW, Egan PA. (2005). Hepatitis C virus envelope proteins regulate CHOP via induction of the unfolded protein response. FASEB J 19: 1510–12.
Cheng EH, Wei MC, Weiler S, et al. (2001). BCL-2, BCL-X(L) sequester BH3 domain-only molecules preventing BAX- and BAK-mediated mitochondrial apoptosis. Mol Cell 8:705–11.
Cheng G, Feng Z, He B. (2005). Herpes simplex virus 1 infection activates the endoplasmic reticulum resident kinase PERK and mediates eIF-2alpha dephosphorylation by the gamma(1)34.5 protein. J Virol 79:1379–88.
Cho HK, Cheong KJ, Kim HY, Cheong J. (2011). Endoplasmic reticulum stress induced by hepatitis B virus X protein enhances cyclo-oxygenase 2 expression via activating transcription factor 4. Biochem J 435:431–9.
Choukhi A, Ung S, Wychowski C, Dubuisson J. (1998). Involvement of endoplasmic reticulum chaperones in the folding of hepatitis C virus glycoproteins. J Virol 72:3851–8.
Ciczora Y, Callens N, Séron K, et al. (2010). Identification of a dominant endoplasmic reticulum-retention signal in yellow fever virus pre-membrane protein. J Gen Virol 91:404–14.
DeDiego ML, Nieto-Torres JL, Jimenez-Guardeno JM, et al. (2011). Severe acute respiratory syndrome coronavirus envelope protein regulates cell stress response and apoptosis. PLoS Pathog 7:e1002315.
de Haan CA, Rottier PJ. (2005). Molecular interactions in the assembly of coronaviruses. Adv Virus Res 64:165–230.
Dimcheff DE, Askovic S, Baker AH, et al. (2003). Endoplasmic reticulum stress is a determinant of retrovirus-induced spongiform neurodegeneration. J Virol 77:12617–29.
Dimcheff DE, Faasse MA, McAtee FJ, Portis JL. (2004). Endoplasmic reticulum (ER) stress induced by a neurovirulent mouse retrovirus is associated with prolonged BiP binding and retention of a viral protein in the ER. J Biol Chem 279:33782–90.
Edgil D, Polacek C, Harris E. (2006). Dengue virus utilizes a novel strategy for translation initiation when cap-dependent translation is inhibited. J Virol 80:2976–86.
Einav S, Sobol, HD, Gehrig E, Glenn JS. (2010). The Hepatitis C Virus (HCV) NS4B RNA Binding Inhibitor Clemizole Is Highly Synergistic with HCV Protease Inhibitors. J Infect Dis 202:65–74.
Elgadi MM, Hayes CE, Smiley JR. (1999). The herpes simplex virus vhs protein induces endoribonucleolytic cleavage of target RNAs in cell extracts. J Virol 73:7153–64.
Gaddy DF, Lyles DS. (2005). Vesicular stomatitis viruses expressing wild-type or mutant M proteins activate apoptosis through distinct pathways. J Virol 79:4170–9.
Galindo I, Hernaez B, Munoz-Moreno R, et al. (2012). The ATF6 branch of unfolded protein response and apoptosis are activated to promote African swine fever virus infection. Cell Death Dis 3:e341.
Galluzzi L, Brenner C, Morselli E, et al. (2008). Viral control of mitochondrial apoptosis. PLoS Pathog 4:e1000018.
Garcia MA, Meurs EF, Esteban M. (2007). The dsRNA protein kinase PKR: virus and cell control. Biochimie 89:799–811.
Ghendon Y, Markushin S, Heider H, et al. (1986). Haemagglutinin of Influenza A Virus Is a Target for the Antiviral Effect of NorakinR. J Gen Virol 67:1115–22.
Gong G, Waris G, Tanveer R, Siddiqui A. (2001). Human hepatitis C virus NS5A protein alters intracellular calcium levels, induces oxidative stress, and activates STAT-3 and NF-κB. Proc Natl Acad Sci U S A 98: 9599–604.
Gotoh T, Terada K, Oyadomari S, Mori M. (2004). hsp70-DnaJ chaperone pair prevents nitric oxide- and CHOP-induced apoptosis by inhibiting translocation of Bax to mitochondria. Cell Death Differ 11:390–402.
Harding HP, Novoa I, Zhang Y, et al. (2000). Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol Cell 6:1099–108.
Hase T, Summers PL, Ray P, Asafo-Adjei E. (1992). Cytopathology of PC12 cells infected with Japanese encephalitis virus. Virchows Arch B Cell Pathol Incl Mol Pathol 63:25–36.
Hassan IH, Zhang MS, Powers LS, et al. (2012). Influenza A Viral replication is blocked by inhibition of the inositol-requiring enzyme 1 (IRE1) stress pathway. J Biol Chem 287:4679–89.
He B. (2006). Viruses, endoplasmic reticulum stress, and interferon responses. Cell Death Differ 13:393–403.
He B, Gross M, Roizman B. (1997). The gamma(1)34.5 protein of herpes simplex virus 1 complexes with protein phosphatase 1alpha to dephosphorylate the alpha subunit of the eukaryotic translation initiation factor 2 and preclude the shutoff of protein synthesis by double-stranded RNA-activated protein kinase. Proc Natl Acad Sci U S A 94:843–8.
Hegde NR, Chevalier MS, Wisner TW, et al. (2006). The role of BiP in endoplasmic reticulum-associated degradation of major histocompatibility complex class I heavy chain induced by cytomegalovirus proteins. J Biol Chem 281:20910–19.
Hetz C. (2012). The unfolded protein response: controlling cell fate decisions under ER stress and beyond. Nat Rev Mol Cell Biol 13: 89–102.
Hollien J, Lin JH, Li H, et al. (2009). Regulated Ire1-dependent decay of messenger RNAs in mammalian cells. J Cell Biol 186:323–31.

Hong JR, Gong HY, Wu JL. (2002). IPNV VP5, a novel anti-apoptosis gene of the Bcl-2 family, regulates Mcl-1 and viral protein expression. Virology 295:217–29.

Hong JR, Huang LJ, Wu JL. (2005). Aquatic birnavirus induces apoptosis through activated caspase-8 and -3 in a zebrafish cell line. J Fish Dis 28:133–40.

Hotamisligil GS. (2010). Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell 140:900–17.

Huang HL, Wu JL, Chen MH, Hong JR. (2011). Aquatic birnavirus-induced ER stress-mediated death signaling contribute to down-regulation of Bcl-2 family proteins in salmon embryo cells. PLoS One 6:e22935.

Inoue T, Tsai B. (2013). How viruses use the endoplasmic reticulum for entry, replication, and assembly. Cold Spring Harb Perspect Biol 5, doi:10.1101/cshperspect.a013250.

Isler JA, Skalet AH, Alwine JC. (2005). Human cytomegalovirus infection activates and regulates the unfolded protein response. J Virol 79:6890–99.

John L, Thomas S, Herchenroder O, et al. (2011). Hepatitis E virus ORF2 protein activates the pro-apoptotic gene CHOP and anti-Apoptotic heat shock proteins. PLoS One 6:e25378.

Jordan R, Wang L, Graczyk TM, et al. (2002). Replication of a cytopathic strain of bovine viral diarrhea virus activates PERK and induces endoplasmic reticulum stress-mediated apoptosis of MDBK cells. J Virol 76:9588–99.

Joyce MA, Walters KA, Lamb SE, et al. (2009). HCV induces oxidative and ER stress, and sensitizes infected cells to apoptosis in SCID/Alb-uPA mice. PLoS Pathog 5:e1000291.

Keay S, Baldwin BR, Smith MW, et al. (1995). Increases in [Ca2+]i mediated by the 92.5-kDa putative cell membrane receptor for HCMV gp86. Am J Physiol 269:C11–21.

Kim HT, Waters K, Stoica G, et al. (2004). Activation of endoplasmic reticulum stress signaling pathway is associated with neuronal degeneration in MoMuLV-ts1-induced spongiform encephalomyelopathy. Lab Invest 84:816–27.

Knoops K, Kikkert M, Worm SH, et al. (2008). SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. PLoS Biol 6:e226.

Kuo CY, Tsai JI, Chou TY, et al. (2012). Apoptosis induced by hepatitis B virus X protein in a CCL13-HBx stable cell line. Oncol Rep 28: 127–32.

Lazar C, Macovei A, Petrescu S, Branza-Nichita N. (2012). Activation of ERAD pathway by human hepatitis B virus modulates viral and subviral particle production. PLoS One 7:e34169.

Lee AH, Iwakoshi NN, Glimcher LH. (2003). XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. Mol Cell Biol 23:7448–59.

Lee DY, Sugden B. (2008a). The latent membrane protein 1 oncogene modifies B-cell physiology by regulating autophagy. Oncogene 27: 2833–42.

Lee DY, Sugden B. (2008b). The LMP1 oncogene of EBV activates PERK and the unfolded protein response to drive its own synthesis. Blood 111:2280–9.

Lee YH, Wei CW, Wang JJ, Chiou CT. (2011). Rana catesbeiana ribonuclease inhibits Japanese encephalitis virus (JEV) replication and enhances apoptosis of JEV-infected BHK-21 cells. Antiviral Res 89: 193–8.

Leung HJ, Duran EM, Kurtoglu M, et al. (2012). Activation of the unfolded protein response by 2-deoxy-D-glucose inhibits kaposi's sarcoma-associated herpesvirus replication and gene expression. Antimicrob Agents Chemother 56:5794–803.

Leyssen P, De Clercq E, Neyts J. (2000). Perspectives for the treatment of infections with Flaviviridae. Clin Microbiol Rev 13:67–82.

Li B, Gao B, Ye L, et al. (2007). Hepatitis B virus X protein (HBx) activates ATF6 and IRE1-XBP1 pathways of unfolded protein response. Virus Res 124:44–9.

Li J, Liu Y, Wang Z, et al. (2011). Subversion of cellular autophagy machinery by hepatitis B virus for viral envelopment. J Virol 85: 6319–33.

Li S, Ye L, Yu X, et al. (2009). Hepatitis C virus NS4B induces unfolded protein response and endoplasmic reticulum overload response-dependent NF-kappaB activation. Virology 391:257–64.

Li S, Yu X, Guo Y, Kong L. (2012). Interaction networks of hepatitis C virus NS4B: implications for antiviral therapy. Cell Microbiol 14: 994–1002.

Li XD, Lankinen H, Putkuri N, et al. (2005). Tula hantavirus triggers pro-apoptotic signals of ER stress in Vero E6 cells. Virology 333: 180–9.

Limjindaporn T, Wongwiwat W, Noisakran S, et al. (2009). Interaction of dengue virus envelope protein with endoplasmic reticulum-resident chaperones facilitates dengue virus production. Biochem Biophys Res Commun 379:196–200.

Lin JH, Walter P, Yen TS. (2008). Endoplasmic reticulum stress in disease pathogenesis. Annu Rev Pathol 3:399–425.

Lindl KA, Akay C, Wang Y, et al. (2007). Expression of the endoplasmic reticulum stress response marker, BiP, in the central nervous system of HIV-positive individuals. Neuropathol Appl Neurobiol 33:658–69.

Liu N, Kuang X, Kim HT, et al. (2004). Possible involvement of both endoplasmic reticulum- and mitochondria-dependent pathways in MoMuLV-ts1-induced apoptosis in astrocytes. J Neurovirol 10: 189–98.

Machamer CE, Doms RW, Bole DG, et al. (1990). Heavy chain binding protein recognizes incompletely disulfide-bonded forms of vesicular stomatitis virus G protein. J Biol Chem 265:6879–83.

Mao H, Palmer D, Rosenthal KS. (2001). Changes in BiP (GRP78) levels upon HSV-1 infection are strain dependent. Virus Res 76:127–35.

Marciniak SJ, Yun CY, Oyadomari S, et al. (2004). CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. Genes Dev 18:3066–77.

Martin-Latil S, Mousson L, Autret A, et al. (2007). Bax is activated during rotavirus-induced apoptosis through the mitochondrial pathway. J Virol 81:4457–64.

Medigeshi GR, Lancaster AM, Hirsch AJ, et al. (2007). West Nile virus infection activates the unfolded protein response, leading to CHOP induction and apoptosis. J Virol 81:10849–60.

Merquiol E, Uzi D, Mueller T, et al. (2011). HCV causes chronic endoplasmic reticulum stress leading to adaptation and interference with the unfolded protein response. PLoS One 6:e24660.

Minakshi R, Padhan K, Rani M, et al. (2009). The SARS Coronavirus 3a protein causes endoplasmic reticulum stress and induces ligand-independent downregulation of the type 1 interferon receptor. PLoS One 4:e8342.

Moradpour D, Penin F, Rice CM. (2007). Replication of hepatitis C virus. Nat Rev Microbiol 5:453–63.

Mulvey M, Arias C, Mohr I. (2007). Maintenance of endoplasmic reticulum (ER) homeostasis in herpes simplex virus type 1-infected cells through the association of a viral glycoprotein with PERK, a cellular ER stress sensor. J Virol 81:3377–90.

Mulvey M, Poppers J, Sternberg D, Mohr I. (2003). Regulation of eIF2α Phosphorylation by Different Functions That Act during Discrete Phases in the Herpes Simplex Virus Type 1 Life Cycle. J Virol 77: 10917–28.

Nakhasi HL, Ramanujam M, Atreya CD, et al. (2001). Rubella virus glycoprotein interaction with the endoplasmic reticulum calreticulin and calnexin. Arch Virol 146:1–14.

Netherton CL, Parsley JC, Wileman T. (2004). African swine fever virus inhibits induction of the stress-induced proapoptotic transcription factor CHOP/GADD153. J Virol 78:10825–8.

Nie Z, Phenix BN, Lum JJ, et al. (2002). HIV-1 protease processes procaspase 8 to cause mitochondrial release of cytochrome c, caspase cleavage and nuclear fragmentation. Cell Death Differ 9:1172–84.

Nivitchanyong T, Tsai YC, Betenbaugh MJ, Oyler GA. (2009). An improved in vitro and in vivo Sindbis virus expression system through host and virus engineering. Virus Res 141:1–12.

Novoa I, Zeng H, Harding HP, Ron D. (2001). Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2alpha. J Cell Biol 153:1011–22.

Ohoka N, Yoshii S, Hattori T, et al. (2005). TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. EMBO J 24:1243–55.

Oostra M, te Lintelo EG, Deijs M, et al. (2007). Localization and membrane topology of coronavirus nonstructural protein 4: involvement of the early secretory pathway in replication. J Virol 81: 12323–36.

Pasqual G, Burri DJ, Pasquato A, et al. (2011). Role of the host cell's unfolded protein response in arenavirus infection. J Virol 85:1662–70.

Pavio N, Romano PR, Graczyk TM, et al. (2003). Protein synthesis and endoplasmic reticulum stress can be modulated by the hepatitis C virus envelope protein E2 through the eukaryotic initiation factor 2alpha kinase PERK. J Virol 77:3578–85.

Pena J, Harris E. (2011). Dengue virus modulates the unfolded protein response in a time-dependent manner. J Biol Chem 286:14226–36.

Perry JW, Ahmed M, Chang KO, et al. (2012). Antiviral activity of a small molecule deubiquitinase inhibitor occurs via induction of the unfolded protein response. PLoS Pathog 8:e1002783.

Qian Z, Xuan B, Gualberto N, Yu D. (2011). The human cytomegalovirus protein pUL38 suppresses endoplasmic reticulum stress-mediated cell death independently of its ability to induce mTORC1 activation. J Virol 85:9103–13.

Rathore AP, Ng ML, Vasudevan SG. (2013). Differential unfolded protein response during Chikungunya and Sindbis virus infection: CHIKV nsP4 suppresses eIF2alpha phosphorylation. Virol J 10:36.

Rider TH, Zook CE, Boettcher TL, et al. (2011). Broad-spectrum antiviral therapeutics. PLoS One 6:e22572.

Rivera J, Abrams C, Hernaez B, et al. (2007). The MyD116 African swine fever virus homologue interacts with the catalytic subunit of protein phosphatase 1 and activates its phosphatase activity. J Virol 81:2923–29.

Ritzenthaler C, Laporte C, Gaire F, et al. (2002). Grapevine fanleaf virus replication occurs on endoplasmic reticulum-derived membranes. J Virol 76:8808–19.

Roberson EC, Tully JE, Guala AS, et al. (2012). Influenza induces endoplasmic reticulum stress, caspase-12-dependent apoptosis, and c-Jun N-terminal kinase-mediated transforming growth factor-beta release in lung epithelial cells. Am J Respir Cell Mol Biol 46:573–81.

Robert F, Kapp LD, Khan SN, et al. (2006). Initiation of protein synthesis by Hepatitis C virus Is refractory to reduced eIF2 · GTP · Met-tRNAiMet ternary complex availability. Mol Biol Cell 17:4632–44.

Rodrigues R, Paranhos-Baccala G, Vernet G, Peyrefitte CN. (2012). Crimean-Congo hemorrhagic fever virus-infected hepatocytes induce ER-stress and apoptosis crosstalk. PLoS One 7:e29712.

Ron D, Hampton RY. (2004). Membrane biogenesis and the unfolded protein response. J Cell Biol 167:23–5.

Schroder M, Kaufman RJ. (2005). The mammalian unfolded protein response. Annu Rev Biochem 74:739–89.

Schweizer M, Peterhans E. (1999). Oxidative stress in cells infected with bovine viral diarrhoea virus: a crucial step in the induction of apoptosis. J Gen Virol 80:1147–55.

Shaffer AL, Shapiro-Shelef M, Iwakoshi NN, et al. (2004). XBP1, downstream of Blimp-1, expands the secretory apparatus and other organelles, and increases protein synthesis in plasma cell differentiation. Immunity 21:81–93.

Shah AC, Parker JN, Shimamura M, Cassady KA. (2009). Spontaneous and engineered compensatory HSV mutants that counteract the host antiviral PKR response. Viruses 1:510–22.

Sharon-Friling R, Goodhouse J, Colberg-Poley AM, Shenk T. (2006). Human cytomegalovirus pUL37x1 induces the release of endoplasmic reticulum calcium stores. Proc Natl Acad Sci U S A 103: 19117–22.

Sidrauski C, Walter P. (1997). The transmembrane kinase Ire1p is a site-specific endonuclease that initiates mRNA splicing in the unfolded protein response. Cell 90:1031–9.

Skaletskaya A, Bartle LM, Chittenden T, et al. (2001). A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation. Proc Natl Acad Sci U S A 98:7829–34.

Su HL, Liao CL, Lin YL. (2002). Japanese Encephalitis Virus infection initiates endoplasmic reticulum stress and an unfolded protein response. J Virol 76:4162–71.

Su YC, Wu JL, Hong JR. (2011). Betanodavirus up-regulates chaperone GRP78 via ER stress: roles of GRP78 in viral replication and host mitochondria-mediated cell death. Apoptosis 16:272–87.

Suhy DA, Giddings Jr TH, Kirkegaard K. (2000). Remodeling the endoplasmic reticulum by poliovirus infection and by individual viral proteins: an autophagy-like origin for virus-induced vesicles. J Virol 74:8953–65.

Sun CC, Thorley-Lawson DA. (2007). Plasma cell-specific transcription factor XBP-1s binds to and transactivates the Epstein-Barr virus BZLF1 promoter. J Virol 81:13566–77.

Sun M, Rothermel TA, Shuman L, et al. (2004). Conserved cysteine-rich domain of paramyxovirus simian virus 5 V protein plays an important role in blocking apoptosis. J Virol 78:5068–78.

Sung SC, Chao CY, Jeng KS, et al. (2009). The 8ab protein of SARS-CoV is a luminal ER membrane-associated protein and induces the activation of ATF6. Virology 387:402–13.

Szegezdi E, Logue SE, Gorman AM, Samali A. (2006). Mediators of endoplasmic reticulum stress-induced apoptosis. EMBO Rep 7: 880–5.

Tabas I, Ron D. (2011). Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. Nat Cell Biol 13:184–90.

Tabata Y, Takano K, Ito T, et al. (2007). Vaticanol B, a resveratrol tetramer, regulates endoplasmic reticulum stress and inflammation. Am J Physiol Cell Physiol 293:C411–8.

Tardif KD, Mori K, Kaufman RJ, Siddiqui A. (2004). Hepatitis C virus suppresses the IRE1-XBP1 pathway of the unfolded protein response. J Biol Chem 279:17158–64.

Taylor GM, Raghuwanshi SK, Rowe DT, et al. (2011). Endoplasmic reticulum stress causes EBV lytic replication. Blood 118:5528–39.

Tirosh B, Iwakoshi NN, Lilley BN, et al. (2005). Human cytomegalovirus protein US11 provokes an unfolded protein response that may facilitate the degradation of class I major histocompatibility complex products. J Virol 79:2768–79.

Tolonen N, Doglio L, Schleich S, Krijnse Locker J. (2001). Vaccinia virus DNA replication occurs in endoplasmic reticulum-enclosed cytoplasmic mini-nuclei. Mol Biol Cell 12:2031–46.

Trujillo-Alonso V, Maruri-Avidal L, Arias CF, Lopez S. (2011). Rotavirus infection induces the unfolded protein response of the cell and controls it through the nonstructural protein NSP3. J Virol 85: 12594–604.

Umareddy I, Pluquet O, Wang QY, et al. (2007). Dengue virus serotype infection specifies the activation of the unfolded protein response. Virol J 4:91.

Urano F, Wang X, Bertolotti A, et al. (2000). Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. Science 287:664–6.

Urban C, Rheme C, Maerz S, et al. (2008). Apoptosis induced by Semliki Forest virus is RNA replication dependent and mediated via Bak. Cell Death Differ 15:1396–407.

van Kuppeveld FJ, Hoenderop JG, Smeets RL, et al. (1997). Coxsackievirus protein 2B modifies endoplasmic reticulum membrane and plasma membrane permeability and facilitates virus release. EMBO J 16:3519–32.

Ventoso I, Sanz MA, Molina S, et al. (2006). Translational resistance of late alphavirus mRNA to eIF2alpha phosphorylation: a strategy to overcome the antiviral effect of protein kinase PKR. Genes Dev 20: 87–100.

Versteeg GA, van de Nes PS, Bredenbeek PJ, Spaan WJ. (2007). The coronavirus spike protein induces endoplasmic reticulum stress and upregulation of intracellular chemokine mRNA concentrations. J Virol 81:10981–90.

von dem Bussche A, Machida R, Li K, et al. (2010). Hepatitis C virus NS2 protein triggers endoplasmic reticulum stress and suppresses its own viral replication. J Hepatol 53:797–804.

Walter P, Ron D. (2011). The unfolded protein response: from stress pathway to homeostatic regulation. Science 334:1081–6.

Watowich SS, Morimoto RI, Lamb RA. (1991). Flux of the paramyxovirus hemagglutinin-neuraminidase glycoprotein through the endoplasmic reticulum activates transcription of the GRP78-BiP gene. J Virol 65:3590–7.

Wu HC, Wu JL, Chu HL, et al. (2010). RGNNV induces mitochondria-mediated cell death via newly synthesized protein dependent pathway in fish cells. Fish Shellfish Immunol 29:451–63.

Wu YP, Chang CM, Hung CY, et al. (2011). Japanese encephalitis virus co-opts the ER-stress response protein GRP78 for viral infectivity. Virol J 8:128.

Xu X, Zhang H, Zhang Q, et al. (2013a). Porcine epidemic diarrhea virus E protein causes endoplasmic reticulum stress and up-regulates interleukin-8 expression. Virol J 10:26.

Xu X, Zhang H, Zhang Q, et al. (2013b). Porcine epidemic diarrhea virus N protein prolongs S-phase cell cycle, induces endoplasmic reticulum stress, and up-regulates interleukin-8 expression. Vet Microbiol 164: 212–21.

Xuan B, Qian Z, Torigoi E, Yu D. (2009). Human cytomegalovirus protein pUL38 induces ATF4 expression, inhibits persistent JNK phosphorylation, and suppresses endoplasmic reticulum stress-induced cell death. J Virol 83:3463–74.

Yamaguchi H, Wang HG. (2004). CHOP is involved in endoplasmic reticulum stress-induced apoptosis by enhancing DR5 expression in human carcinoma cells. J Biol Chem 279:45495–502.

Yan W, Frank CL, Korth MJ, et al. (2002). Control of PERK eIF2alpha kinase activity by the endoplasmic reticulum stress-induced molecular chaperone P58IPK. Proc Natl Acad Sci U S A 99:15920–5.

Ye C, Dickman MB, Whitham SA, et al. (2011). The unfolded protein response is triggered by a plant viral movement protein. Plant Physiol 156:741–55.

Ye J, Rawson RB, Komuro R, et al. (2000). ER stress induces cleavage of membrane-bound ATF6 by the same proteases that process SREBPs. Mol Cell 6:1355–64.

Yee J, White RE, Anderton E, Allday MJ. (2011). Latent Epstein-Barr virus can inhibit apoptosis in B cells by blocking the Induction of NOXA Expression. PLoS One 6:e28506.

Yoshida H, Matsui T, Yamamoto A, et al. (2001). XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. Cell 107:881–91.

Yu CY, Hsu YW, Liao CL, Lin YL. (2006). Flavivirus infection activates the XBP1 pathway of the unfolded protein response to cope with endoplasmic reticulum stress. J Virol 80:11868–80.

Yu H, Li S, Yang C, et al. (2011). Homology model and potential virus-capsid binding site of a putative HEV receptor Grp78. J Mol Model 17:987–95.

Zhang HM, Ye X, Su Y, et al. (2010). Coxsackievirus B3 infection activates the unfolded protein response and induces apoptosis through downregulation of p58IPK and activation of CHOP and SREBP1. J Virol 84:8446–59.

Zhang K, Kaufman RJ. (2008). From endoplasmic-reticulum stress to the inflammatory response. Nature 454:455–62.

Zhong Y, Liao Y, Fang S, et al. (2012). Up-regulation of Mcl-1 and Bak by coronavirus infection of human, avian and animal cells modulates apoptosis and viral replication. PLoS One 7:e30191.