 doi:10.20944/preprints202007.0190.v1

Review

Emerging role of the integrated stress response upon viral infection

Yongshu Wu[1,3], Xiaodong Qin[1], Meera Prajapati[1], Yijing Li[3], Zhidong Zhang[1,2] and Yanmin Li[1,2*]

[1] State Key Laboratory of Veterinary Etiological Biology, Lanzhou Veterinary Research Institute, Chinese Academy of Agricultural Sciences, Lanzhou 730046, Gansu, China; wysh0224@163.com(Y.W.); qinxiaodong@caas.cn(X.D.); prajapatim@hotmail.com(M.P.); zhangzhidong@caas.cn(Z.Z.)
[2] College of Life Science and Technology, Southwest Minzu University, Chengdu, Sichuan, 610041, China
[3] College of Veterinary Medicine, Northeast Agricultural University, Harbin, Heilongjiang, 150030, China; yijingli@163.com(Y.L.)
* correspondence: liyanmin@caas.cn; Tel.: +86-0931-8399328

Received: ; Accepted: ; Published:

Abstract: The integrated stress response (ISR) is an adaptational signaling pathway that is induced in response to different stimuli, such as accumulation of unfolded and misfolded protein, hypoxia, amino acid deprivation, viral infection and ultraviolet light. It has been known that viral infection can activate ISR, but the role of ISR during viral infection is still unclear. In some cases, ISR is a protective mechanism of host cell against infection with virus whilst ISR may be hijacked by viruses for facilitating its replication. In this review, we highlighted recent advances on induction of ISR upon viral infection and the downstream responses involved such as autophagy, apoptosis, formation of stress granules and innate immunity response. We then discussed the molecular mechanism of ISR regulating viral replication and how viruses antagonize this cellular stress response resulting from ISR.

Keywords: integrated stress response; eIF2α phosphorylation; unfolded protein response; viral replication; host

1. Introduction

The integrated stress response (ISR) is an intricate signaling pathway existing in eukaryotic cells which is activated through the phosphorylation of eukaryotic translation initiation factor 2 alpha (eIF2α) in response to different physiological changes and pathological conditions. Activation of ISR results in decrease of global protein synthesis and induction of selected genes, such as transcription factor 4 (ATF4). It is speculated that the ISR ultimate destiny is determined by intensity and duration of stress, level of eIF2α phosphorylation and ATF4 activation [1]. Initially a pro-survival effect is activated, and intracellular hemostasis is reconstructed under short-term stress. However, a cell death program is initiated when cells are exposed to a prolonged and severe stress [1-3]. It has been well known that viral infection could induce ISR, but the role of ISR is still less defined. In some cases, ISR is a protective mechanism against virus replication, while in other cases, ISR may be hijacked by the virus to facilitate its replication. In this review, we summarized current knowledge of the molecular mechanisms of ISR with an emphasis on how cells initiate ISR, how viral factors modulate the ISR and the downstream cellular responses, as well as how the ISR pathway determine cell prognosis upon viral infection.

2. Overview of the integrated stress response signaling pathway

In physiological condition, eIF2 consisting of eIF2α, eIF2β and eIF2γ, possess both phosphorylation sites and RNA binding sites. eIF2 forms a ternary complex with GTP and Met-tRNAi, and then binds 40S ribosome subunit, resulting in the formation of 43S pre-initiation complex (PIC)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 July 2020 doi:10.20944/preprints202007.0190.v1

with two small initiation factors (eIF1 and eIF1A) [4,5]. PIC is recruited to the 5'methylguanine cap of mRNA through the eIF4F complex, the latter contains eIF4G and eIF4E. PIC migrates to the AUG start codon and then binds the Met-tRNAi anti-codon and the AUG start codon which facilitates protein synthesis. AUG recognition causes arrest of the scanning PIC and triggers conversion of eIF2 GDP-bound state via gated phosphate (Pi) release and GTPase-activating (GAP)factor eIF5. eIF2-GDP complex dissociate from 40S ribosomal complex and transforms to GTP with the help of eIF2B complex and enters another recycling of initiation of mRNA translation [6,7]. In stress condition, phosphorylated eIF2 is fully capable of forming an initiation-competent eIF2-TC, but following its release, phosphorylated eIF2-GDP tightly binds to and sequesters the guanine nucleotide exchange factor eIF2B, abrogating its activity. Most mRNA translation is reduced when eIF2α is phosphorylated. However, translation from certain mRNAs with at least two upstream open reading frames (uORFs) of appropriate type and position can be upregulated. The best-characterized mammalian examples are ATF4, ATF5 and CHOP. Upregulation of ATF4, ATF5 and CHOP function activates chaperon proteins to promote cellular recovery or activate cell death pathways upon sustained stress.

In mammalian cells, ISR kinases act as an early responder to restore cellular homeostasis upon different stimuli. There are four members of ISR family: general control nonderepressible 2 (GCN2), PKR-like ER kinase (PERK), the heme-regulated inhibitor (HRI) and the interferon (IFN)-induced double-stranded RNA-dependent protein kinase (PKR). Actually, each kinase can sense distinct stresses, because they share homological catalytic domains but possess unique regulatory domains [8,9]. ISR is activated by any of the four members of eIF2α kinases family in response to various stress stimuli, GNC2 is sensitive to amino acid starvation, PERK is induced by the accumulation of unfolded or misfolded proteins in the ER, HRI is activated in response to heme deficiency, and PKR is activated by double stranded RNA (dsRNA) [10]. Schematic diagram of protein structure of eIF2α kinase family is shown in **Figure 1**.

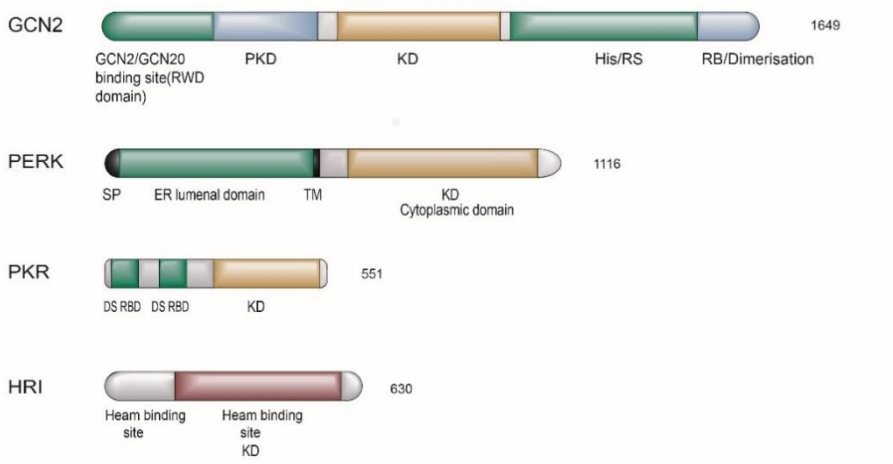

Figure 1. Schematic diagram of protein structure of eIF2α kinase family. Four kinases contain different regulation structure domains and binds to various ligands to deliver signals.

Normally, PERK is bound by 78-KDa glucose-regulated protein (GRP78) in the ER membrane. However, two models for PERK activation during ER stress has been put forward. In the classical model, misfolded or unfolded protein gets accumulated in the ER lemon and then GRP78 dissociates from PERK resulting in its autophosphorylation and oligomerization. Activation of PERK phosphorylates eIF2α at serine 51, which halts overall protein translation and selected gene ATF4 is upregulated to restore cellular recovery [1]. Eukaryotic cells employ three different mechanisms to deal with unfolded proteins and misfolded proteins in the ER: transcriptional induction of chaperons, protein degradation, and translational attenuation [11]. In all these processes, ATF4 is a vital point to determine cell prognosis. During amino acid starvation, ATF4 activates upregulation of several genes involved in autophagy, including ATF3, ATF5 and ATF7, which is a pro-survival

signaling [12]. Transcriptional ATF4 can induce expression of genes for pro-autophagy or anti-apoptosis to restore hemostasis upon different stress, such as regulating development and DNA damage response1, anti-apoptotic myeloid cell leukemia-1 [13-15]. A cell death signaling would occur when an adaptive response failed to restore hemostasis. Transcriptional ATF4 and its downstream genes are induced, particularly ATF3 and C/EBP homologous protein (CHOP) and a pro-apoptosis signaling is generated through the formation of heterodimeric with ATF3 or CHOP. It then activate transcriptional factor expression of Bcl-2 homology3 (BH3)-only pro-apoptotic protein NOXA [16].

PKR protein which is mainly located in the cytosol and the nucleus, phosphorylate eIF2α after viral infection resulting in inhibition of viral mRNA translation and induction of apoptosis. PKR is the eIF2α kinase which is the most well studied in terms of structures and activation mechanism. PKR is comprised of kinase domain along with the other eIF2α kinases, and two dsRNA binding domains (dsRBD) modulating its activity. In non-stressed cells, PKR exists in the form of monomeric because of auto-inhibitory effect of its dsRBD. Following interaction with dsRNA molecules through the two N-terminal dsRNA-binding motifs (dsRBM) of dsRBD, PKR auto-phosphorylates on Thr446, and then phosphorylates eIF2α, which leads to a dramatic inhibition of cell protein synthesis to reduce the protein flux into the ER and viral mRNA synthesis [17-19], similarly, ATF4 also play an important role in regulating cellular and initiating downstream signaling of ISR in these processed. However, few studies have indicated that PKR is also activated by oxidation, ER stress, cytokine signaling, growth and so on [20-22].

HRI is expressed mainly in erythrocytes [23], and also present in liver and macrophages [8]. HRI ensures production of α- and β-chains of globin and balance the heme in red blood cells [8]. HRI binds to heme at its N-terminus and is activated through autophosphorylation in response to low level of heme and then phosphorylates eIF2α [24-26]. HRI can also be induced by other stresses, including heat shock, osmotic pressure, oxidative stress induced by arsenite and bacterial pathogens [27-30]. However, there is no report about induction of HRI upon viral infection in mammal animal cells.

Amino acid exhaust activates GCN2 through the increasing of deacylated tRNA molecules [31]. GCN2 is also activated upon glucose deprivation, ultraviolet irradiation, hypoxia and viral infection though the mechanism remains to be defined [32-35].

The kinases of ISR can be activated simultaneously upon stimuli, such as, viral infection can result in simultaneous activation of PERK, GCN2, as well as PKR [35-37]. In addition, four eIF2α kinases are also induced upon oxidative stress [3,38,39].

Dephosphorylation of eIF2α is a terminal signal of ISR and cell return to normal protein translation and synthesis. The process is mediated by growth arrest and DNA damage-inducible protein (GADD34) and constitutive repressor of eIF2α phosphorylation, which interact with protein phosphatase 1 (PP1) and restore protein synthesis and normal cellular function. GADD34 is a downstream production of eIF2α phosphorylation and ATF4 at late stage of the ISR, so GADD34 plays a pivotal role as a negative feedback loop in attenuating signaling of ISR [1,40].

3. Virus modulation of ISR signaling pathway

3.1. Virus modulation of ISR signaling pathway through the control of the ISR-associated kinases activity

Many viruses can activate ISR pathway in infected cells through different mechanism（Table 1）. Generally, viruses hijack cellular protein synthesis mechanism for their own protein expression which may disrupt the ER homeostasis [41]. Meanwhile, viruses also develop mechanisms that manipulate host ISR signaling pathway to promote viral translation and persistence during viral infection [42,43]. In general, ISR activation is triggered by virulent or pathogenic viruses instead of inactivated viruses suggesting that the activation of ISR is associated with viral replication [44]. However, inactivated foot-and-mouth disease virus (FMDV) has been reported to induce eIF2α-ATF4 pathway [45].

Table 1. Molecular Mechanism of ISR upon Viral Infection.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 July 2020 doi:10.20944/preprints202007.0190.v1

Virus	Type of virus	Activation of UPR branch	Activation of ISR kinases	Activation mechanism	References
TGEV	A single-stranded positive-sense RNA	PERK, IRE1a, ATF6	PERK, PKR	TGEV replication is inhibited through activation of NF-κB, which facilitate type I IFN production, and PERK-eIF2α-P induce overall attenuation of protein translation.	Mei Xue, *et al*. 2018; Jazmina L. G. Cruz, *et al*. 2010.
SARS-CoV	A single-stranded positive-sense RNA		PERK, PKR	Viral replication is do not influenced by both kinases, apoptosis is induced by PKR kinase.	Verena Kra¨hling, *et al*. 2009.
IBV	A single-stranded positive-sense RNA		PERK, PKR	IBV infection causes ER stress and induces PERK phosphorylation. Phosphorylation of eIF2α by PERK and PKR induces the expression of ATF4, ATF3, and GADD153. GADD153 exerts its proapoptotic activities via suppressing Bcl2 and antagonizing the survival kinases (ERKs) by inducing TRIB3.	Ying Liao, *et al*. 2013
PEDV	A single-stranded positive-sense RNA	PERK, IRE1a, ATF6	PERK	Inhibit viral replication through PERK-eIF2α-P induced overall attenuation of protein translation.	Yue Wang. *et al*. 2014.
BTV	Double stranded RNA	PERK,	PERK	BTV induce ER stress mediates autophagy via the PERK-eIF2α pathway and contributes to BTV1 replication.	Shuang Lv, *et al*. 2015
HCV	A single-stranded positive-sense RNA	PERK, ATF6	PERK,	HCV core protein induce autophagy and UPR induced autophagy promote viral replication through PERK and ATF6 pathways.	J. Wang, *et al*. 2015.
EMCV	A single-stranded positive-sense RNA	PERK, ATF6	PERK	2C and 3D protein of EMCV induce autophagy and UPR induced autophagy promote viral replication through PERK and ATF6 pathways.	Lei Hou, *et al*. 2014.
BVDV	A single-stranded positive-sense RNA		PERK	BVDV infection induce pro-apoptosis process through PERK-eIF2α pathway, which leads to expression of CHOP, caspase12 and PARP.	Jordan, R. *et al*. 2002.

 doi:10.20944/preprints202007.0190.v1

DENV	A single-stranded positive-sense RNA	PERK, IRE1a, ATF6	PERK	PERK signaling is induced at the early stage of DENV2 infection, IRE1a and ATF6 pathways are activated at late stage, which leads to the expression of GADD34 and CHOP that resulting in apoptosis. DENV-induced autophagy promotes viral replication through forming the autophagosome, which provide a dock and energy for viral replication.	Pena, J, *et al*. 2011; Umareddy *et al*, 2007; Yu *et al*, 2006. Lee, Y. R. *et al*. 2018; Datan, E. *et al*.2016.
WNV	A single-stranded positive-sense RNA	PERK, IRE1a, ATF6	PERK	Limit viral replication.	Medigeshi, G. R, *et al*. 2007.
HSV	Double stranded DNA	PERK, PKR	PERK, PKR	PKR is induced firstly, and PERK is activated when viral protein accumulates in ER. Activation of PERK and PKR phosphorylate eIF2α to block translation of viral protein. However, $\gamma_1$34.5 protein of HSV promote viral replication through recruiting PP1 to dephosphorylate eIF2α. Us11 and ICP34.5 protein of HSV-1 can block activation of PKR-eIF2α signaling pathway and regulate autophagy by binding directly PKR-binding domain and binding to Beclin1 respectively to promote viral replication.	Guofeng Cheng, *et al*.2005. Marion Lussignol, *et al*. 2013.
PCV2	A single-stranded circular DNA	PERK	PERK	Cap protein of PCV2 activate UPR-induced apoptosis via PERK-eIF2α-ATF4-CHOP-Bcl-2 axis. Meanwhile, PCV2 can utilize UPR to promote viral replication and expression of Cap protein.	Yingshan Zhou, *et al*. 2016; Ying-shan ZHOU. *et al*. 2017.
JEV	A single-stranded positive-sense RNA		PKR	JEV infection induce PKR at the late stage.	Tu YC, *et al*. 2012.
WNV	A single-stranded positive-		PKR	WNV infection induce PKR at the late stage.	Samuel MA, *et al*. 2006.

	sense RNA				
SINV	A single-stranded positive-sense RNA		PKR GCN2	SINV infection induce PKR kinase. SINV infection induce GCN2. Meanwhile, GCN2 inhibit early viral translation and prevent viral replication through activation of eIF2α phosphorylation.	Domingo-Gil E, *et al*. 2011. Gorchakov R, *et al*. 2004; Juan J Berlanga. *et al.* 2006.
SFV	A single-stranded positive-sense RNA		PKR	SFV infection induce PKR kinase.	Ventoso I, *et al*. 2006.
EV71	A single-stranded positive-sense RNA		PKR	EV71 infection induce typical SGs through PKR pathway. However, EV71 induced SG-like structures are antiviral RNA granules to suppress viral propagation.	Yuanmei Zhu, *et al*. 2016. Hua Zhang , *et al*. 2016
PFV	A positive sense single-stranded RNA virus	PERK, IRE1a, ATF6	PERK	PFV induce a complete autophagic process through UPRs, increasing activation of autophagy inhibit viral replication.	Peipei Yuan. *et, al.* 2017.
MNV	A positive sense single-stranded RNA virus		PKR	MNV infection induce PKR pathway and eIF2α phosphorylation. NS3 protein of MNV control host protein translation. Meanwhile, MNV recruit G3BP1 to promote viral replication and prevent SGs formation.	Svenja Fritzlar, *et al.* 2019.

3.1.1. PERK kinase

Many viral proteins are synthesized in the ER, consequently, the induction of ER stress is a common outcome. It was found that PERK axis of unfolded protein response (UPR) plays an important role in regulation of viral protein synthesis under ER stress. Bluetongue virus (BTV), hepatitis C virus (HCV), encephalomyocarditis virus (EMCV), dengue virus (DENV) infection were able to induce UPR-induced autophagy to promote viral replication [46-50]. Porcine circovirus type 2 (PCV2) cap protein was involved in activating UPR-induced apoptosis and deploys UPR to enhance viral replication through PERK-eIF2α-ATF4-CHOP-Bcl2 signaling pathway [51,52]. Likewise, Bovine viral diarrhea virus (BVDV) and WNV also activate UPR-induced apoptosis through PERK pathway, however its effect on the replication of WNV and BVDV is yet unclear [53,54]. It is suggested that the synthesis of these viral proteins is associated with ER and ISR initiates downstream signaling pathways to restore cellular hemostasis. Meanwhile, viruses utilize the activation of ISR to promote viral replication. Coronavirus replication is also closely associated with ER stress. Gastroenteritis virus (TGEV) infection was found to activate all three UPR pathways through upregulation of GRP78, but PERK-eIF2α branch mainly suppress viral replication through inducing IFN-I production and

 doi:10.20944/preprints202007.0190.v1

eIF2α phosphorylation-mediated global attenuation of protein translation occurred during TGEV infection in vitro and in vivo [55].

In contrast, another study showed that TGEV infection was only able to induce the PKR-eIF2α signaling pathway [56]. The reason for this discrepancy was unclear but it might be due to the different TGEV strains used in those two studies. In addition, both PERK and PKR pathway axis are induced by other coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV), but the viral replication is not influenced by these kinases [57]. Infectious bronchitis virus (IBV) infection activated PERK/PKR kinases and viral replication may be promoted through GADD153-dependent apoptosis [55,58,59]. HSV-1 also regulates autophagy to promote its replication through PKR pathway [37].

3.1.2. PKR kinase

Among ISR-associated four kinases, PKR has been found to play an important role in antiviral host defense due to its induction by IFN [60]. PKR is also activated by dsRNA but mostly from by-products of viral replication or transcription. In RNA virus, dsRNA replicative formations are obligatory intermediates for synthesis of new genomic RNA copies. For DNA viruses, vaccinia virus (VV), adenovirus and herpes simplex virus (HSV) possess ORFs in opposite orientation and produce overlapping mRNA transcripts and then fold to form dsRNA stretches that activate PKR [36,60]. Japanese encephalitis virus (JEV) and West Nile virus (WNV), belonging to positive-sense RNA, induce PKR at the late stage of viral infection [61,62], this could be due to the time required for the conversion of ssRNA to dsRNA and the activity of PKR is blocked upon viral infection. PKR is also induced by Sindbis virus (SINV) and Semliki Forest virus (SFV) [63-65]. In general, global protein translation is blocked upon viral infection, including viral protein replication. However, Murine norovirus (MNV) infection induces PKR signaling pathway and leads to eIF2α phosphorylation and global protein translation shutoff which does not impact viral replication because NS3 protein of MNV disturb in host protein translational efficiency. It is suggested that viruses control host translational mechanism for itself. Meanwhile, MNV promote viral replication and prevent SGs formation through recruiting G3BP1 protein to the site of viral replication complex [66].

3.1.3. HRI kinase

To date, there is no evidence that HRI can be activated upon virus infection in mammal cells. HRI of *Epinephelus coioides* (EcHRI), a homologue gene in fish, is changed at the transcription level upon red-spotted grouper nervous necrosis virus (RGNNV) infection and inhibit viral replication through upregulating the expression of IFN-related cytokines which indicates the potential role of HRI in antiviral response [67].

3.1.4. GCN2 kinase

The role of GCN2 against RNA viruses is yet to be known. GCN2 is specifically induced through phosphorylation of eIF2α at early stage of SINV infection. During that mechanism, two nonadjacent regions of SINV genomic bind to histidyl-tRNA synthetase-related domain of GCN2 and meanwhile, GCN2 block early viral translation of genomic SINV by eIF2α phosphorylation induced by the activation of GCN2 [35,68].

3.2. Viral proteins which directly regulate integrated stress response signaling axis

Viruses develop different mechanisms to manipulate ISR signaling pathway to promote viral translation and persistence during viral infection [42,43]. In order to facilitate replication, both DNA and RNA viruses encode proteins to selectively regulate ISR pathway, enhance ER protein folding capacity and metabolic regulation of cells. M protein of vesicular stomatitis virus (VSV) is responsible for counteracting antiviral response of eIF2α phosphorylation [69]. NS5A protein and E2 protein of HCV were found to interfere PKR and PERK kinase respectively which leads to inhibition of downstream eIF2α phosphorylation and helps in viral replication [70,71], whereas in JEV, NS2A

 doi:10.20944/preprints202007.0190.v1

protein was found to inhibit PKR-induced eIF2 α phosphorylation [61,71]. Influenza A virus non-structural protein 1 (IAV-NS1) limit eIF2α phosphorylation through hampering PKR dimerization and autophosphorylation [72]. Upon DENV infection, PERK-induced eIF2α phosphorylation is suppressed through upregulating expression of GADD34, which interacts with PP1 to dephosphorylate eIF2α [73]. Protein 7 of TGEV and M protein of VSV antagonize eIF2α phosphorylation during infection [56,69]. PKR is induced at early stage of HSV infection, activation of PKR phosphorylates eIF2α and block protein translation, including viral protein, PERK is activated during viral protein accumulation, however, $\gamma_1$34.5 protein of HSV inhibit PERK phosphorylation to promote viral replication. Meanwhile, the expression of GADD34 binds in an eIF2α-independent mechanism to PP1 and mediate in dephosphorylation of eIF2α. It is speculated that $\gamma_1$34.5 protein may recruit PP1 to dephosphorylate eIF-2 and antagonizes the activities of both PKR and PERK [37].

3.3. Modulation of down-streaming signaling of ISR upon viral infection

ISR is activated through eIF2α phosphorylation during viral infection, which leads to translation arrest of both cellular protein and viral protein, meanwhile, phosphorylated eIF2α initiate downstream signaling of ISR to regulate viral replication and restore cellular homeostasis, such as autophagy, formation of SGs, apoptosis and innate immunity response.

3.3.1. Inducation of autophagy through ISR

Autophagy exerts a pro-survival signaling to facilitate cell metabolic homeostasis. Although the functions between UPR and autophagy are independent, many studies showed that the activation of UPR regulates autophagy and further control viral replication and pathogenic mechanism during viral infection.

Autophagy could be activated through UPR signaling pathway during viral infection. It was found that autophagy response could benefit viral replication during DENV2 infection. Further analysis showed that PERK-eIF2α-ATF4-ATG12 and IRE1α-JNK-BECLIN1 signaling pathway was mainly involved in this process. IRE1α-JNK induced Bcl-2 phosphorylation to release Beclin1 which triggered autophagic activity. PERK-eIF2 α -ATF4-ATG12 signaling pathway partly effect on autophagy at early stage of DENV infection [49]. Another report showed that PERK signaling pathway participates in DENV-induced autophagy and enhance viral replication in dog MDCK and mouse MEFs [50], mounting results also demonstrated that DENV-induced autophagy promotes viral replication through forming the autophagosome, which provide a dock and energy for viral replication. Meanwhile, DENV capsid protein promote viral replication by altering lipid biosynthesis derived from ER membrane which alleviates ER stress and promote cell survival [50,74,75]. This phenomenon is also common in other members of *flaviviriuses* family, such as HCV, JEV and WNV [76-78] indicating that DEVN and other members of *flaviviriuses* family are ER-tropic viruses that accomplish translation, replication and package in the ER.

Other viruses also induce autophagy through UPRs to enhance viral replication. BTV infection induce autophagy through PERK-eIF2α pathway and in turn autophagy promotes viral replication [46,79]. Similarly duck enteritis virus (DEV) activates autophagy to benefit its replication through PERK-eIF2α-ATF4 and IRE1-XBP1 signaling pathways [80]. Autophagy is induced during Newcastle disease virus (NDV) infection and promotes its replication. Studies have further shown that P and NP proteins of NDV induce autophagy via PERK and ATF6 pathways [81]. A complete autophagy is induced by HCV core protein and CHOP plays a vital role in UPR autophagy signaling. [82]In addition, UPR associated autophagy has been found to promote viral replication through PERK-eIF2α-ATF4 and ATF6 signaling pathways activating ATF4 and CHOP enhance the expression of ATG12 and LC3B, which benefits autophagic process [11,70,83]. EMCV infection induces autophagy through PERK and ATF6 pathways via viral 2C and 3C protein, which promote viral replication [47,84]. Autophagy is induced via ER stress during coxsackievirus (CV) B3 infection, and three branches of UPR participate in regulation of autophagy [85]. These results suggest that viruses can induce autophagy through UPR to promote mainly viral replication. It is speculated that UPR-induced autophagy may promote cellular survival and restore homeostasis.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 July 2020 doi:10.20944/preprints202007.0190.v1

However, prototype foamy virus (PFV) infection can induce a complete autophagic process through ER stress containing PERK, IRE1 and ATF6 branches, and increasing activation of autophagy inhibit PFV replication which implies that PFV-induced autophagy has a novel mechanism and plays an antiviral role in viral replication [86]. eIF2α-ATF4 pathway is induced through inhibition of AKT-MTOR signaling pathway during FMDV infection by VP2 protein interacting with heat shock protein family B small member1 (HSPB1) in mammal cells [45].

PKR is induced by dsRNA and reduces translation of viral mRNAs to protect cells [36]. PKR is also required for nutrient deprivation and viral-induced autophagy [10]. PKR-eIF2α signaling is activated during HSV-1 infection but the role of autophagy in HSV-1 replication is unclear. However, Us11 protein of HSV-1 can block activation of PKR-eIF2α signaling by binding directly to PKR-binding domain [10,87], and ICP34.5 of HSV-1 also regulate autophagy through dephosphorylation of eIF2α and binding to Beclin1 to promote viral replication [88,89]. These findings indicate that autophagy has an antiviral effect against HSV-1.

Overall, eIF2α phosphorylation serves as the central link between viral infection and induction of autophagy. Interestingly, the other branches of UPR also involve in activation of autophagy during viral infection thereby indicating that viral-induced autophagy mediated by ER stress is a pro-survival cellular process at the early stage of viral infection and a cell death signaling may be initiated in case of severe viral infection. However, the underlying mechanism of how UPR stress regulates viral induced autophagy remains unclear. The above findings are summarized (Figure 2).

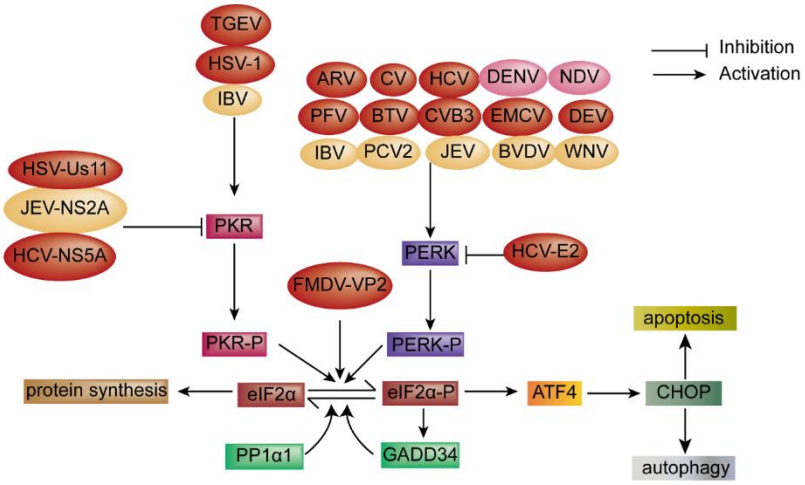

Figure 2. Diagram of the ISR signaling pathway, autophagy and apoptosis during viral infection. Autophagy: autophagy is activated through PERK/PKR-eIF2α pathway upon TGEV, HSV-1, ARV, CV, HCV, PFV, BTV, CVB3, EMCV and DEV infection, FMDV-VP2 induces autophagy through interaction with HSPB1 and activation of the eIF2α-ATF4 pathway. In turn, HSV-Us11, HCV-NS5A and HCV-E2 protein block autophagy (red). **Apoptosis:** apoptosis is induced via PERK/PKR-eIF2α pathway under IBV, PCV2, BVDV, JEV, WNV infection. Oppositely, JEV-NS2A inhibit apoptosis (yellow). In addition, autophagy and apoptosis simultaneously are induced through PERK -eIF2α pathway during the same virus infection, such as DENV and NDV (pink).

3.3.2. Formation of SGs through ISR

SGs are the accumulation of cytoplasmic non-membrane structures of mRNA-binding proteins (mRNPs) and related proteins in response to stress stimuli. The mechanism for protein translation inhibition mainly by eIF2α phosphorylation at Ser-51 leads to an increase of mRNA released from polysomes [90]. It has been proposed that four kinases phosphorylate eIF2α and lead to the formation of SGs. On the other hand, SGs formation is independent of eIF2α phosphorylation, such as disruption of eIF4A helicase by pateamine A and the eIF4F complex by H_2O_2 which implies that SGs composition and assembly differ in a stress-dependent manner [91-93]. SGs are formed in response

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 July 2020 doi:10.20944/preprints202007.0190.v1

to various stresses in mammalian cells, including oxidative stress, energy depletion, UV irradiation, hypoxia, ER stress and viral infection [92-94].

The virus requires cellular translation machinery to synthesize its proteins in host cells. However, SGs formation results from global translation repression of mRNAs and blocks viral gene expression during viral infection. Thus, SGs formation may be the result of an innate immune response [95]. Moreover, virus also take measures to confront these adverse conditions and maximizes replication efficiency through inhibition of SGs formation and disruption of PBs assembly [96]. Therefore, the illumination of the relationship between SGs and virus is very important to understand the interaction of host and viruses [96].

eIF2α is phosphorylated through PKR branch during MNV infection causing stoppage of protein translation but without inhibiting viral protein replication because MNV suppress cytokine translation and the formation of SGs to promote viral replication. MNV infection does not induce SGs formation. However, MNV recruits SGs nucleating protein G3BP1 to enhance viral replication and prevent SGs formation. This suggests that MNV promote viral replication through PKR-P-eIF2α-SGs axis and evade innate immune response [66]. The similar phenomenon was observed in FMDV where FMDV infection does not induce SGs formation. Instead L^{pro} of FMDV actively antagonize SGs formation and cleave SGs scaffold proteins Ras-GAP SH3 domain binding protein1 (G3BP1) and G3BP2 but not T-cell-restricted intracellular antigen1 (TIA-1). Additionally, L^{pro} had no effect on PKR activation and eIF2α phosphorylation. Enteroviruses71 (EV71) infection was able to induce formation of typical SGs (tSGs) via the PKR-eIF2α pathway. Further, SG-like structures also are induced which is a different canonical SGs and is an antiviral structures to suppress EV71 propagation [97]. However, $2A^{pro}$ of EV71 block tSGs formation and transforms from tSGs to atypical SGs (aSGs) through cleaving eIF4GI. 2Apro regulates SGs formation which is also common in picornaviruses [55,98]. Several studies demonstrated that the composition of SGs is different from FMDV L^{pro} and EV $2A^{pro}$ infection, but the exact composition of aSGs remains unclear [97,99,100].

IAV deficient in NS1, induce cytoplasmic granules termed as antiviral stress granules (avSGs) which is different from the canonical SGs. IAVA-NS1 infection inhibit formation of avSGs and production of IFN through PKR-eIF2α signaling pathway [101]. SINV, EMCV, Adenovirus, HCV and NDV also trigger avSGs implying that avSGs may play an important role in detection of viruses to initiate antiviral signaling. NS1 protein of IAV block the formation of SGs and the activation of IFN genes [94]. Interestingly, SGs might provide a platform for interaction between virus and host antiviral molecules and help in the removal of viruses.

EMCV was able to transiently induce SGs formation through PKR signaling at early infection, however, EMCV 3C protein was found to inhibit SGs formation via cleaving G3BP1 at late stage of infection. Similarly, 3C protein of poliovirus (PV) and L protein of Theiler's murine encephalomyelitis virus (TMEV) were able to inhibit SGs formation [100,102,103]. These findings indicate that picornaviruses also use the same strategy to evade immune response by targeting G3BP1 which is essential for efficient induction of IFN-β.

HCV infection triggers eIF2α phosphorylation and SGs formation depending on PKR branch [104]. In addition, SGs formation is induced through PKR-P-eIF2α-SGs pathway by respiratory syncytial virus (RSV), VV, measles virus (MeV) and human immunodeficiency virus (HIV), C protein-deficient Sendai virus (SeV), tick-borne encephalitis virus (TBEV), SINV, EV71 and PV infection [105-111]. It is suggested that PKR-P-eIF2α-SGs pathway is an important signaling for SGs formation. SGs formation is activated through eIF2α phosphorylation upon reovirus infection, however, which kinase is induced in this process remain unknown [112]. PERK-P-eIF2α-SGs signaling pathway is induced during human cytomegalovirus (HCMV) infection and GCN2-P-eIF2α-SGs branch is activated during SINV infection [35,113]. Hence, ISR kinases are involved in SGs formation during viral infection and play an important role in antiviral defense and restoring cell homeostasis.

Recent studies have demonstrated that different viral infection can induce or inhibit the formation of SGs such as Flaviviridae virus, rotavirus, Junin virus, mouse hepatitis virus (MHV), HIV-1, nervous necrosis virus (NNV), VSV, MRV and HSV [105,114-120]. Furthermore, SGs

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 9 July 2020 doi:10.20944/preprints202007.0190.v1

formation is induced or inhibited at different stage of a viral replication cycle or via different signaling pathway such as SFV, HCV and RSV [121]. Emerging evidence suggests that eIF2α-SGs signaling pathway plays a pivotal role in innate immunity maintaining cell hemostasis. The summary of SGs formation during viral infection is shown (Figure3).

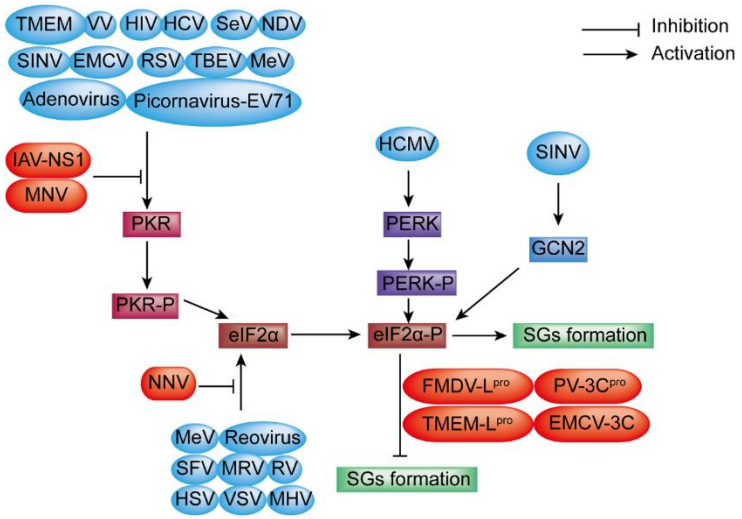

Figure 3. Diagram of the ISR signaling pathway and SGs formation under viral infection. EV71, VV, HIV, HCV, SeV, EMCV, RSV, TBEV, MeV, TMEM, Adenovirus, NDV and SINV infection promote SGs formation through PKR-eIF2α-P signaling pathway. MeV, Reovirus, SFV, RV, HSV, VSV, MHV and MRV trigger eIF2α phosphorylation and benefit for SGs formation (blue). However, IAV-NS1, MNV, NNV, FMDV-L^{pro}, PV-$3C^{pro}$, TMEM-L^{pro} and EMCV-3C infection inhibit SGs formation (red). SGs formation is increased via PERK-eIF2α-P branch during HCMV infection. SINV infection enhance SGs formation through GCN2- eIF2α-P branch.

3.3.3. Activation of Apoptosis through ISR

Apoptosis, a programing cell death, is supposed to be a host strategy to combat viral infection. PERK/PKR-eIF2α-ATF4 pathway is activated during the early stage of IBV infection in Vero cells and H1299 cells which results in expression of ATF4, ATF3 and GADD153. Activated GADD153 induce a ER stress-mediated pro-apoptotic pathway through suppressing Bcl2 and antagonizing the survival kinases (ERKs) by inducing tribbles homolog3 (TRIB3) [59]. Similarly, studies have shown that ER stressor IRE1α is also activated in IBV-infected cells and serves as a survival factor during coronavirus infection [59,122,123]. HCV triggers apoptosis through induction of GADD153 and ER calcium depletion [113,124-126]. JEV infection triggers UPR and apoptosis through expression of GADD153 and p38 kinase. However, which branch is induced remains unknown [127]. Cap protein of PCV2 induces UPR and then results in apoptosis through PERK-eIF2α-ATF4-CHOP-Bcl-2 signaling pathway which reduces Bcl2 expression and increases caspase3 enhancing the viral replication [51,52]. Some viruses of *Flaviviridae* family also induce apoptosis. A pro-apoptosis response is induced through PERK-eIF2α pathway which leads to expression of CHOP, caspase12 and poly ADP ribose polymerase (PARP) and downregulation of Bcl2 such as NS protein of WNV, BVDV and DENV [53] [54,73,128]. Three branches of UPR involve in NDV-induced apoptosis and CHOP is initiated by PERK/PKR-eIF2α signaling to promote viral proliferation [129]. Overall, UPR-induced apoptosis is activated through PERK-eIF2α-ATF4-CHOP signaling upon viral infection. Activation of CHOP leads to suppression of Bcl2 and induction of GADD34 and plays a pro-survival function. However, eIF2α-ATF4-GADD153 pathway may inhibit viral replication during a prolong stress condition. Hence, CHOP may serve as a pro-apoptosis or pro-survival function depending on the condition of stress. In addition, IRE1α modulates Akt and JNK kinases to promote cell survival. UPR-induced apoptosis is summarized (Figure2).

 doi:10.20944/preprints202007.0190.v1

3.4. Role of ISR in antiviral response

Apart from the importance of ISR on restoring cell homeostasis, ISR kinases also play a vital role in innate immunity during viral infection which is thought to function as an antiviral pathway [95,130]. Kinases of ISR phosphorylate eIF2α and block overall protein translation including viral protein. Hence, this process is an antiviral response. SGs formation results in global translation repression of mRNAs including viral protein. In this process, PKR plays important role because it can directly recruit the formation of SGs. Thus, SGs formation is also an innate immune response to viral infection [95]. However, some viruses were able to avoid antiviral response of ISR to promote its replication. MNV infection leads to eIF2α phosphorylation through PKR pathway and block translational shutoff of host cell protein. At the same time, the translation of IFN-α, IFN-β and IL-6 are suppressed to promote MNV replication which is also an immune evasion strategy [66]. Furthermore, other members of ISR kinases are also involved in antiviral immune response. NF-κB is activated and IFN-I are produced through PERK-eIF2α axis during TGEV infection which represents a characterizing role of virus-induced UPR in NF-κB activation during other viral infection [55]. On the other hand, GCN2 plays a novel role in the antiviral response to certain RNA viruses. As mentioned above, GCN2 block the translation of viral protein and further prevent replication of SINV through eIF2α phosphorylation [35].

4. Discussion

ISR is a protective response and is induced by different kinds of stresses which leads to the inhibition of overall protein translation and the preferential transcription of targeting genes through eIF2α phosphorylation to restore cellular hemostasis. ISR is firstly observed in 2002 because ISR is a hub for many signaling pathways that converge on eIF2α phosphorylation such as autophagy, apoptosis, SGs formation, cell hemostasis and innate immunity response. However, there is a great gap about ISR and how eIF2α kinases are activated and the genes of downstream of eIF2α determine cell prognosis during viral infection. Generally, a pro-survival response is induced in a short and mild stress to restore cell homeostasis but a cell death signaling is activated during long and severe stress. However, the mechanism of the switch between pro-survival and cell death signaling needs to be further illuminated.

eIF2α phosphorylation is the core of ISR and inhibit viral protein synthesis to restore cellular homeostasis during viral infection. Activation of eIF2α phosphorylation initiate downstream mechanism through UPR, autophagy, apoptosis and formation of SGs. UPR-induced these responses regulate viral replication to alleviate stress. PERK-eIF2α pathway plays an important role in benefiting viral replication and other branches of UPR are also involved. It is speculated that viruses may take some strategies to promote viral protein synthesis and UPR-related autophagy is a novel mechanism for regulating viral replication. These phenomena infer that autophagy has the dual role in regulating viral replication. PKR plays a vital role in virus-induced SGs formation. Not only in eIF2α phosphorylation and inhibition of viral replication, but it also provides a platform to promote IFN gene production [114,131]. The leader protein of EMCV can inhibit IFN gene activation [103] and some viruses can disturb in the formation of SGs [102]. PERK-eIF2α signaling pathway and CHOP-mediated apoptosis are very vital during viral infection. The levels of viral protein expression and virus titer are increased in CHOP-deficient cells thereby indicating that both ISR pathway and CHOP expression enhance antiviral response [54].

On contrary, viruses use different strategies to promote viral protein synthesis. For example, M protein of VSV can counteract antiviral response. Chikungunya virus (CHIKV) and VSV antagonize phosphorylation of eIF2α [69,132]. In addition, some viruses switch translation mode from an eIF2-dependent to an eIF2-independent process to ensure efficient replication such as PV and EV [133,134]. It was reported that DENV infection inhibit PERK-mediated eIF2α phosphorylation by elevating the expression of GADD34 which interacts with PP1 to dephosphorylate eIF2α [73]. However, the conversion mechanism of viral replication through ISR remains unclear.

Recently, emerging evidence showed that ISR, autophagy and apoptosis are induced simultaneously during viral infection [71,135]. It was reported that a complete autophagy could be

induced during HCV infection and CHOP played a pivotal role in the ISR autophagy pathway [82]. Further study showed that HCV core protein activated autophagy through PERK-eIF2α-ATF4 and ATF6 pathways and facilitated ATG12 and LC3 protein expression via ATF4 and CHOP [48]. Hence, ISR is a complicated and integrated signaling response.

Activation of PERK phosphorylates eIF2α to induce ISR upon ER stress and ATF4 is a vital point to determine cell prognosis in this process [1]. We speculate that ISR is a part of UPR^{ER}, and both are induced upon stresses including viral infection but the mechanism between UPR^{ER} and ISR remains unknown. Numerous studies demonstrated that upregulation of eIF2α phosphorylation and induction of ISR during UPR^{MT} which inhibits protein synthesis and is required for preferential synthesis of ATF4, ATF5 and CHOP to recover mitochondria function [136-138]. Hence, the role of eIF2α in UPR^{MT} and the mechanism of UPR^{MT} under viral infection also need to be illuminated [139]. We speculate that ISR, synergizing with UPR^{ER} and UPR^{MT} plays an important and integrated role in maintaining cellular homeostasis and promoting cell survival against viral infection.

In conclusion, the role of ISR is becoming more and more important during viral infection. ISR is a complicated, integrated and a pro-survival cellular response that converge on eIF2α phosphorylation. PERK-eIF2α signaling pathway plays vital role in regulation of viral replication and UPR-induced autophagy. PKR-eIF2α signaling pathway mediates mainly in the formation of SGs and CHOP controls UPR-induced apoptosis. Meanwhile, other branches of UPR is also involved in this process. However, many mechanisms of ISR remain unclear. Hence, further investigations are highly essential to understand the mechanism of ISR upon viral infection. In addition, it is also necessary to understand that how viruses take measures to modulate ISR to promote own replication and virulence which is vital to illuminate the interaction between host and viruses and as a therapeutic target to enhance host defense against viruses.

Author Contributions: YM: ZD and XD conceived the idea, revised and edited the manuscript. YS collected information and drafted the manuscript. ZD and XD performed the structural analysis. All authors read and made final approval of the manuscript.

Funding: This work was supported by the National Key R & D Program of China (2016YFD0500108; 2016YFE0204100) and the International Cooperation Project of CAAS Innovation Program (CAAS-GJHZ201700X).

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Pakos-Zebrucka, K.; Koryga, I.; Mnich, K.; Ljujic, M.; Samali, A.; Gorman, A.M. The integrated stress response. *EMBO Rep* **2016**, *17*, 1374-1395.
2. Ron, D. Translational control in the endoplasmic reticulum stress response. *J Clin Invest* **2002**, *110*, 1383-1388.
3. Harding, H.P.; Zhang, Y.; Zeng, H.; Novoa, I.; Lu, P.D.; Calfon, M.; Sadri, N.; Yun, C.; Popko, B.; Paules, R., *et al*. An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. *Mol Cell* **2003**, *11*, 619-633.
4. Aitken, C.E.; Lorsch, J.R. A mechanistic overview of translation initiation in eukaryotes. *Nat Struct Mol Biol* **2012**, *19*, 568-576.
5. Lomakin, I.B.; Steitz, T.A. The initiation of mammalian protein synthesis and mrna scanning mechanism. *Nature* **2013**, *500*, 307-311.
6. Jackson, R.J.; Hellen, C.U.; Pestova, T.V. The mechanism of eukaryotic translation initiation and principles of its regulation. *Nat Rev Mol Cell Biol* **2010**, *11*, 113-127.
7. Hinnebusch, A.G.; Lorsch, J.R. The mechanism of eukaryotic translation initiation: New insights and challenges. *Cold Spring Harb Perspect Biol* **2012**, *4*, a011544.

8. Donnelly, N.; Gorman, A.M.; Gupta, S.; Samali, A. The eif2alpha kinases: Their structures and functions. *Cell Mol Life Sci* **2013**, *70*, 3493-3511.
9. Lavoie, H.; Li, J.J.; Thevakumaran, N.; Therrien, M.; Sicheri, F. Dimerization-induced allostery in protein kinase regulation. *Trends Biochem Sci* **2014**, *39*, 475-486.
10. Lussignol, M., Queval, C., Bernet-Camard, M. F., Cotte-Laffitte, J., Beau, I., Codogno, P., et al. The herpes simplex virus 1 us11 protein inhibits autophagy through its interaction with the protein kinase pkr. *J Virol* **2013**, *87*, 859-871.
11. Tardif, K.D.; Mori, K.; Siddiqui, A. Hepatitis c virus subgenomic replicons induce endoplasmic reticulum stress activating an intracellular signaling pathway. *J Virol* **2002**, *76*, 7453-7459.
12. B'Chir, W., Maurin, A. C., Carraro, V., Averous, J., Jousse, C., Muranishi, Y., et al. The eif2alpha/atf4 pathway is essential for stress-induced autophagy gene expression. *Nucleic Acids Res* **2013**, *41*, 7683-7699.
13. Dennis, M.D.; McGhee, N.K.; Jefferson, L.S.; Kimball, S.R. Regulated in DNA damage and development 1 (redd1) promotes cell survival during serum deprivation by sustaining repression of signaling through the mechanistic target of rapamycin in complex 1 (mtorc1). *Cell Signal* **2013**, *25*, 2709-2716.
14. Whitney, M.L.; Jefferson, L.S.; Kimball, S.R. Atf4 is necessary and sufficient for er stress-induced upregulation of redd1 expression. *Biochem Biophys Res Commun* **2009**, *379*, 451-455.
15. Hu, J., Dang, Nana., Menu, Eline., De Bryune, Elke., Xu, Dehui., Van Camp, Ben., et al. . Activation of atf4 mediates unwanted mcl-1 accumulation by proteasome inhibition. *Blood* **2012**, *119*, 826-837.
16. Wang, Q.Y., Mora-Jensen, H., Weniger, M. A., Perez-Galan, P., Wolford, C., Hai, T., et al. Erad inhibitors integrate er stress with anepigenetic mechanism to activate bh3-onlyprotein noxa in cancer cells. *PNAS.* **2009**, *106*, 2200-2205.
17. Galabru, J.; Hovanessian, A. Autophosphorylation of the protein kinase dependent on double-stranded rna. *J Biol Chem* **1987**, *262*, 15538-15544.
18. Rhoads, R.E. Regulation of eukaryotic protein synthesis by initiation factors. *J Biol Chem* **1993**, *268*, 3017-3020.
19. Dey, M., Cao, C., Dar, A. C., Tamura, T., Ozato, K., Sicheri, F., et al. Mechanistic link between pkr dimerization, autophosphorylation, and eif2alpha substrate recognition. *Cell* **2005**, *122*, 901-913.
20. Nakamura, T.; Furuhashi, M.; Li, P.; Cao, H.; Tuncman, G.; Sonenberg, N.; Gorgun, C.Z.; Hotamisligil, G.S. Double-stranded rna-dependent protein kinase links pathogen sensing with stress and metabolic homeostasis. *Cell* **2010**, *140*, 338-348.
21. Onuki, R.; Bando, Y.; Suyama, E.; Katayama, T.; Kawasaki, H.; Baba, T.; Tohyama, M.; Taira, K. An rna-dependent protein kinase is involved in tunicamycin-induced apoptosis and alzheimer's disease. *EMBO J* **2004**, *23*, 959-968.
22. Ruvolo, P.P.; Gao, F.; Blalock, W.L.; Deng, X.; May, W.S. Ceramide regulates protein synthesis by a novel mechanism involving the cellular pkr activator rax. *J Biol Chem* **2001**, *276*, 11754-11758.
23. Crosby, J.S., Lee, K., London, I. M., and Chen, J. J. Erythroid expression of the heme-regulated eif-2a kinase. *molecular and cellular biology* **1994**, *14*, 3906-3914.
24. Bauer, B.N., Kolpin, M. R., Lu, L. R., Han, A. P., and Chen, J. J. Multiple autophosphorylation is essential for the formation of the active andstable homodimer of heme-regulated eif2a kinase. *Biochemistry* **2001**, *40*, 11543-11551.
25. Rafie-Kolpin, M., Chefalo,P.J., Hussain, Z., Hahn, J., Uma, S., Matts,R.L., et al. Two heme-binding

domains of heme-regulated eukaryoticinitiation factor-2a kinase. *J Biol Chem* **2000**, *275*, 5171-5178.

26. Rafie-Kolpin, M., Han A P., and Chen J J. Autophosphorylation of threonine 485 in the activation loop is essential for attaining eif2a kinase activity of hri. *Biochemistry* **2003**, *42*, 6536-6544.
27. Shrestha, N.; Boucher, J.; Bahnan, W.; Clark, E.S.; Rosqvist, R.; Fields, K.A.; Khan, W.N.; Schesser, K. The host-encoded heme regulated inhibitor (hri) facilitates virulence-associated activities of bacterial pathogens. *PLoS One* **2013**, *8*, e68754.
28. McEwen, E.; Kedersha, N.; Song, B.; Scheuner, D.; Gilks, N.; Han, A.; Chen, J.J.; Anderson, P.; Kaufman, R.J. Heme-regulated inhibitor kinase-mediated phosphorylation of eukaryotic translation initiation factor 2 inhibits translation, induces stress granule formation, and mediates survival upon arsenite exposure. *J Biol Chem* **2005**, *280*, 16925-16933.
29. Han, A.P., Yu, C. N., Lu, L. R., Fujiwara, Y., Browne, C., Chin, G., et al. Heme-regulated eif2akinase (hri) is required fortranslational regulation and survival of erythroidprecursors in iron deciency. *EMBO J* **2001**, *20*, 6909-6918.
30. Lu, L.; Han, A.P.; Chen, J.J. Translation initiation control by heme-regulated eukaryotic initiation factor 2alpha kinase in erythroid cells under cytoplasmic stresses. *Mol Cell Biol* **2001**, *21*, 7971-7980.
31. Lageix, S.; Zhang, J.; Rothenburg, S.; Hinnebusch, A.G. Interaction between the trna-binding and c-terminal domains of yeast gcn2 regulates kinase activity in vivo. *PLoS Genet* **2015**, *11*, e1004991.
32. Ye, J.B.; Kumanova, M.; Hart, L.S.; Sloane, K.; Zhang, H.Y.; De Panis, D.N.; Bobrovnikova-Marjon, E.; Diehl, J.A.; Ron, D.; Koumenis, C. The gcn2-atf4 pathway is critical for tumour cell survival and proliferation in response to nutrient deprivation. *Embo Journal* **2010**, *29*, 2082-2096.
33. Grallert, B.; Boye, E. The gcn2 kinase as a cell cycle regulator. *Cell Cycle* **2007**, *6*, 2768-2772.
34. Liu, Y., Laszlo, C., Liu, Y., Liu, W., Chen, X., Evans, S. C., et al. Regulation of g(1) arrest and apoptosis in hypoxia by perk and gcn2-mediated eif2alpha phosphorylation. *Neoplasia* **2010**, *12*, 61-68.
35. Berlanga, J.J., Ventoso, I., Harding, H. P., Deng, J., Ron, D., Sonenberg, N., et al. Antiviral effect of the mammalian translation initiation factor 2alpha kinase gcn2 against rna viruses. *EMBO J* **2006**, *25*, 1730-1740.
36. Garcia, M.A.; Meurs, E.F.; Esteban, M. The dsrna protein kinase pkr: Virus and cell control. *Biochimie* **2007**, *89*, 799-811.
37. Cheng, G.; Feng, Z.; He, B. 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* **2005**, *79*, 1379-1388.
38. Baker, B.M., Nargund, A. M., Sun, T., and Haynes, C. M. Protective coupling of mitochondrial function and protein synthesis via the eif2α kinase gcn-2. *PLoS Genetics* **2012**, *8*, e1002760.
39. Pyo, C.W.; Lee, S.H.; Choi, S.Y. Oxidative stress induces pkr-dependent apoptosis via ifn-γ activation signaling in jurkat t cells. *Biochemical and Biophysical Research Communications* **2008**, *377*, 1001-1006.
40. Novoa, I., Zeng, H. Q., Harding, H.P., and Ron, D. Feedback inhibition of the unfolded protein response by gadd34-mediated dephosphorylation of eif2alpha. *J Cell Biol* **2001**, *153*, 1011-1021.
41. Fung, T.S.; Torres, J.; Liu, D.X. The emerging roles of viroporins in er stress response and autophagy induction during virus infection. *Viruses* **2015**, *7*, 2834-2857.
42. Ambrose, R.L., and Mackenzie, J.M. Flaviviral regulation of the unfolded protein response: Can stress be benefcial? *Future Virol* **2013**, *8*, 1095-1109.
43. Green, A.M.; Beatty, P.R.; Hadjilaou, A.; Harris, E. Innate immunity to dengue virus infection and subversion of antiviral responses. *J Mol Biol* **2014**, *426*, 1148-1160.

44. Neerukonda, S.N.; Katneni, U.K.; Bott, M.; Golovan, S.P.; Parcells, M.S. Induction of the unfolded protein response (upr) during marek's disease virus (mdv) infection. *Virology* **2018**, *522*, 1-12.
45. Sun, P.; Zhang, S.; Qin, X.; Chang, X.; Cui, X.; Li, H.; Zhang, S.; Gao, H.; Wang, P.; Zhang, Z., *et al.* Foot-and-mouth disease virus capsid protein vp2 activates the cellular eif2s1-atf4 pathway and induces autophagy via hspb1. *Autophagy* **2018**, *14*, 336-346.
46. Lv, S.; Sun, E.C.; Xu, Q.Y.; Zhang, J.K.; Wu, D.L. Endoplasmic reticulum stress-mediated autophagy contributes to bluetongue virus infection via the perk-eif2alpha pathway. *Biochem Biophys Res Commun* **2015**, *466*, 406-412.
47. Hou, L., Ge, X. N., Xin, L. X., Zhou, L., Guo, X., and Yang, H. C. Nonstructural proteins 2c and 3d areinvolved in autophagy as induced by the encephalomyocarditis virus. *Virol J* **2014**, *11*, 156.
48. Wang, J., Kang, R., Huang, H., Xi, X., Wang, B., Wang, J., et al. Hepatitis c virus core protein activates autophagy through eif2ak3 and atf6 upr pathway-mediated map1lc3b and atg12 expression. *Autophagy* **2014**, *10*, 766-784.
49. Lee, Y.R., Kuo, S. H., Lin, C. Y., Fu, P. J., Lin, Y. S., Yeh, T. M., et al. Dengue virus-induced er stress is required for autophagy activation, viral replication, and pathogenesis both in vitro and in vivo. *Sci Rep* **2018**, *8*, 489.
50. Datan, E.; Roy, S.G.; Germain, G.; Zali, N.; McLean, J.E.; Golshan, G.; Harbajan, S.; Lockshin, R.A.; Zakeri, Z. Dengue-induced autophagy, virus replication and protection from cell death require er stress (perk) pathway activation. *Cell Death & Disease* **2016**, *7*, e2127-e2127.
51. Zhou, Y., Qi, B., Gu, Y., Xu, F., Du, H., Li, X., et al. Porcine circovirus 2 deploys perk pathway and grp78 for its enhanced replication in pk-15 cells. *Viruses* **2016**, *8*, 56.
52. Zhou, Y.S.; Gu, Y.X.; Qi, B.Z.; Zhang, Y.K.; Li, X.L.; Fang, W.H. Porcine circovirus type 2 capsid protein induces unfolded protein response with subsequent activation of apoptosis. *J Zhejiang Univ Sci B* **2017**, *18*, 316-323.
53. Jordan, R.; Wang, L.; Graczyk, T.M.; Block, T.M.; Romano, P.R. Replication of a cytopathic strain of bovine viral diarrhea virus activates perk and induces endoplasmic reticulum stress-mediated apoptosis of mdbk cells. *J Virol* **2002**, *76*, 9588-9599.
54. Medigeshi, G.R.; Lancaster, A.M.; Hirsch, A.J.; Briese, T.; Lipkin, W.I.; Defilippis, V.; Fruh, K.; Mason, P.W.; Nikolich-Zugich, J.; Nelson, J.A. West nile virus infection activates the unfolded protein response, leading to chop induction and apoptosis. *J Virol* **2007**, *81*, 10849-10860.
55. Xue, M., Fu, F., Ma, Y., Zhang, X., Li, L., Feng, L., et al. The perk arm of the unfolded protein response negatively regulates transmissible gastroenteritis virus replication by suppressing protein translation and promoting type i interferon production. *J Virol* **2018**, *92*, e00431-00418.
56. Cruz, J.L.G., Sola, I., Becares, M., Alberca, B., Plana, J., Luis Enjuanes, L., et al. Coronavirus gene 7 counteracts host defenses and modulates virus virulence. *PLoS Pathogens* **2011**, *7*, e1002090.
57. Krahling, V.; Stein, D.A.; Spiegel, M.; Weber, F.; Muhlberger, E. Severe acute respiratory syndrome coronavirus triggers apoptosis via protein kinase r but is resistant to its antiviral activity. *J Virol* **2009**, *83*, 2298-2309.
58. Fink, S.L., Jayewickreme, T.R., Molony, R.D., Iwawaki, T., Landis, C.S., Lindenbach, B.D., et al. Ire1α promotes viral infection by conferring resistance to apoptosis. *Sci Signal.* **2017**, *10*, 1-30.
59. Liao, Y.; Fung, T.S.; Huang, M.; Fang, S.G.; Zhong, Y.; Liu, D.X. Upregulation of chop/gadd153 during coronavirus infectious bronchitis virus infection modulates apoptosis by restricting activation of the extracellular signal-regulated kinase pathway. *J Virol* **2013**, *87*, 8124-8134.

60. Garcia, M.A., G, il, J., Ventoso, I., Guerra, S., Domingo, E., Rivas, C., et al. Impact of protein kinase pkr in cell biology: From antiviral to antiproliferative action. *Microbiol Mol Biol Rev* **2006**, *70*, 1032-1060.
61. Tu, Y.C.; Yu, C.Y.; Liang, J.J.; Lin, E.; Liao, C.L.; Lin, Y.L. Blocking double-stranded rna-activated protein kinase pkr by japanese encephalitis virus nonstructural protein 2a. *J Virol* **2012**, *86*, 10347-10358.
62. Samuel, M.A.; Whitby, K.; Keller, B.C.; Marri, A.; Barchet, W.; Williams, B.R.; Silverman, R.H.; Gale, M., Jr.; Diamond, M.S. Pkr and rnase l contribute to protection against lethal west nile virus infection by controlling early viral spread in the periphery and replication in neurons. *J Virol* **2006**, *80*, 7009-7019.
63. Domingo-Gil, E.; Toribio, R.; Najera, J.L.; Esteban, M.; Ventoso, I. Diversity in viral anti-pkr mechanisms: A remarkable case of evolutionary convergence. *PLoS One* **2011**, *6*, e16711.
64. Gorchakov, R.; Frolova, E.; Williams, B.R.; Rice, C.M.; Frolov, I. Pkr-dependent and -independent mechanisms are involved in translational shutoff during sindbis virus infection. *J Virol* **2004**, *78*, 8455-8467.
65. Ventoso, I.; Sanz, M.A.; Molina, S.; Berlanga, J.J.; Carrasco, L.; Esteban, M. Translational resistance of late alphavirus mrna to eif2alpha phosphorylation: A strategy to overcome the antiviral effect of protein kinase pkr. *Genes Dev* **2006**, *20*, 87-100.
66. Fritzlar, S., Aktepe, T. E., Chao, Y. W., Kenney, N. D., McAllaster, M. R., Wilen, C. B., et al. Mouse norovirus infection arrests host cell translation uncoupled from the stress granule-pkr-eif2alpha axis. *MBio* **2019**, *10*, e00960-00919.
67. Zang, S.; Zhang, X.; Li, C.; Wang, L.; Wei, J.; Qin, Q. Hri of epinephelus coioides is a critical factor in the grouper immune response to rgnnv infection. *Fish & Shellfish Immunology* **2019**, *87*, 659-668.
68. Krishnamoorthy, J.; Mounir, Z.; Raven, J.F.; Koromilas, A.E. The eif2alpha kinases inhibit vesicular stomatitis virus replication independently of eif2alpha phosphorylation. *Cell Cycle* **2008**, *7*, 2346-2351.
69. Connor, J.H.; Lyles, D.S. Inhibition of host and viral translation during vesicular stomatitis virus infection. Eif2 is responsible for the inhibition of viral but not host translation. *J Biol Chem* **2005**, *280*, 13512-13519.
70. Pavio, N.; Romano, P.R.; Graczyk, T.M.; Feinstone, S.M.; Taylor, D.R. Protein synthesis and endoplasmic reticulum stress can be modulated by the hepatitis c virus envelope protein e2 through the eukaryotic initiation factor 2 kinase perk. *J Virol* **2003**, *77*, 3578-3585.
71. Jheng, J.R.; Ho, J.Y.; Horng, J.T. Er stress, autophagy, and rna viruses. *Front Microbiol* **2014**, *5*, 388.
72. Lu, Y., Wambach, M., Katze, M. G., and Krug, R. M. Binding of the influenza virus ns1 protein to double-stranded rna inhibits the activationof the protein kinase that phosphorylates the eif-2 translation initiation factor. *Virology* **1995**, *214*, 222-228.
73. Pena, J.; Harris, E. Dengue virus modulates the unfolded protein response in a time-dependent manner. *J Biol Chem* **2011**, *286*, 14226-14236.
74. Lee, Y.R.; Lei, H.Y.; Liu, M.T.; Wang, J.R.; Chen, S.H.; Jiang-Shieh, Y.F.; Lin, Y.S.; Yeh, T.M.; Liu, C.C.; Liu, H.S. Autophagic machinery activated by dengue virus enhances virus replication. *Virology* **2008**, *374*, 240-248.
75. <membrane expansion alleviates endoplasmic reticulum stress independently of the unfoldedprotein response.Pdf>.
76. <cellular lipid droplets and hepatitis c virus life cycle.Pdf>.
77. Syed, G.H.; Amako, Y.; Siddiqui, A. Hepatitis c virus hijacks host lipid metabolism. *Trends Endocrinol*

Metab **2010**, *21*, 33-40.

78. Martin-Acebes, M.A.; Blazquez, A.B.; Jimenez de Oya, N.; Escribano-Romero, E.; Saiz, J.C. West nile virus replication requires fatty acid synthesis but is independent on phosphatidylinositol-4-phosphate lipids. *PLoS One* **2011**, *6*, e24970.
79. Lv, S., Xu, Q., Sun, E., Yang, T., Li, J., Feng, Y., et al. Autophagy activated by bluetongue virus infection plays a positive role in its replication. *Viruses* **2015**, *7*, 4657-4675.
80. Yin, H.; Zhao, L.; Jiang, X.; Li, S.; Huo, H.; Chen, H. Dev induce autophagy via the endoplasmic reticulum stress related unfolded protein response. *PLoS One* **2017**, *12*, e0189704.
81. Cheng, J.H., Sun, Y. J., Zhang, F. Q., Zhang, X. R., Qiu, X. S., Yu, L. P., et al. Newcastle disease virus np and p proteins induce autophagy via the endoplasmic reticulum stress-related unfolded protein response. *Sci Rep* **2016**, *6*, 24721.
82. Ke, P.Y.; Chen, S.S. Activation of the unfolded protein response and autophagy after hepatitis c virus infection suppresses innate antiviral immunity in vitro. *J Clin Invest* **2011**, *121*, 37-56.
83. Shrivastava, S.; Bhanja Chowdhury, J.; Steele, R.; Ray, R.; Ray, R.B. Hepatitis c virus upregulates beclin1 for induction of autophagy and activates mtor signaling. *J Virol* **2012**, *86*, 8705-8712.
84. Zhang, Y.; Li, Z.; Ge, X.; Guo, X.; Yang, H. Autophagy promotes the replication of encephalomyocarditis virus in host cells. *Autophagy* **2011**, *7*, 613-628.
85. Luo, X.N., Yao, H. L., Song, J., Song, Q. Q., Shi, B. T., Xia, D., et al. Coxsackievirus b3 infection triggers autophagy through 3 pathways of endoplasmic reticulum stress. *Biomed Environ Sci* **2018**, *31*, 867-875.
86. Yuan, P.; Dong, L.; Cheng, Q.; Wang, S.; Li, Z.; Sun, Y.; Han, S.; Yin, J.; Peng, B.; He, X., *et al.* Prototype foamy virus elicits complete autophagy involving the er stress-related upr pathway. *Retrovirology* **2017**, *14*, 16.
87. Tallo´czy, Z., Jiang, W.X., Virgin IV, H. W., Leib, D. A., Scheuner, D., Kaufman, R.L., et al. Regulation of starvation- and virus-induced autophagy by the eif2alpha kinase signaling pathway. *PNAS.* **2002**, *99*, 190-195.
88. Alexander, D.E.; Ward, S.L.; Mizushima, N.; Levine, B.; Leib, D.A. Analysis of the role of autophagy in replication of herpes simplex virus in cell culture. *J Virol* **2007**, *81*, 12128-12134.
89. Talloczy, Z.; Virgin, H.W.t.; Levine, B. Pkr-dependent autophagic degradation of herpes simplex virus type 1. *Autophagy* **2006**, *2*, 24-29.
90. Kedersha, N.L., Gupta, M., Li, W., Miller, I., and Anderson, P. Rna-binding proteins tia-1 and tiar link the phosphorylation ofeif-2a to the assembly of mammalian stress granules. *The Journal of Cell Biology* **1999**, *147*, 1431-1441.
91. Low, W.K., Dang, Y., Schneider-Poetsch, T., Shi, Z., Choi, N. S., Merrick, W. C., et al. . Inhibition of eukaryotic translation initiation by the marine natural product pateamine a. *Mol Cell* **2005**, *20*, 709-722.
92. Anderson, P.; Kedersha, N. Rna granules. *J Cell Biol* **2006**, *172*, 803-808.
93. Emara, M.M.; Fujimura, K.; Sciaranghella, D.; Ivanova, V.; Ivanov, P.; Anderson, P. Hydrogen peroxide induces stress granule formation independent of eif2alpha phosphorylation. *Biochem Biophys Res Commun* **2012**, *423*, 763-769.
94. Onomoto, K.; Jogi, M.; Yoo, J.S.; Narita, R.; Morimoto, S.; Takemura, A.; Sambhara, S.; Kawaguchi, A.; Osari, S.; Nagata, K., *et al.* Critical role of an antiviral stress granule containing rig-i and pkr in viral detection and innate immunity. *PLoS One* **2012**, *7*, e43031.
95. McCormick, C.; Khaperskyy, D.A. Translation inhibition and stress granules in the antiviral immune response. *Nat Rev Immunol* **2017**, *17*, 647-660.

96. Zhang, Q.; Sharma, N.R.; Zheng, Z.M.; Chen, M. Viral regulation of rna granules in infected cells. *Virol Sin* **2019**, *34*, 175-191.
97. Zhu, Y.; Wang, B.; Huang, H.; Zhao, Z. Enterovirus 71 induces anti-viral stress granule-like structures in rd cells. *Biochem Biophys Res Commun* **2016**, *476*, 212-217.
98. Ye, X.; Pan, T.; Wang, D.; Fang, L.; Ma, J.; Zhu, X.; Shi, Y.; Zhang, K.; Zheng, H.; Chen, H., *et al.* Foot-and-mouth disease virus counteracts on internal ribosome entry site suppression by g3bp1 and inhibits g3bp1-mediated stress granule assembly via post-translational mechanisms. *Front Immunol* **2018**, *9*, 1142.
99. Zhang, H.; Chen, N.; Li, P.; Pan, Z.; Ding, Y.; Zou, D.; Li, L.; Xiao, L.; Shen, B.; Liu, S., *et al.* The nuclear protein sam68 is recruited to the cytoplasmic stress granules during enterovirus 71 infection. *Microb Pathog* **2016**, *96*, 58-66.
100. White, J.P.; Cardenas, A.M.; Marissen, W.E.; Lloyd, R.E. Inhibition of cytoplasmic mrna stress granule formation by a viral proteinase. *Cell Host Microbe* **2007**, *2*, 295-305.
101. Khaperskyy, D.A.; Hatchette, T.F.; McCormick, C. Influenza a virus inhibits cytoplasmic stress granule formation. *FASEB J* **2012**, *26*, 1629-1639.
102. Ng, C.S.; Jogi, M.; Yoo, J.S.; Onomoto, K.; Koike, S.; Iwasaki, T.; Yoneyama, M.; Kato, H.; Fujita, T. Encephalomyocarditis virus disrupts stress granules, the critical platform for triggering antiviral innate immune responses. *J Virol* **2013**, *87*, 9511-9522.
103. Borghese, F.; Michiels, T. The leader protein of cardioviruses inhibits stress granule assembly. *J Virol* **2011**, *85*, 9614-9622.
104. Garaigorta, U.; Heim, M.H.; Boyd, B.; Wieland, S.; Chisari, F.V. Hepatitis c virus (hcv) induces formation of stress granules whose proteins regulate hcv rna replication and virus assembly and egress. *J Virol* **2012**, *86*, 11043-11056.
105. Lindquist, M.E.; Mainou, B.A.; Dermody, T.S.; Crowe Jr, J.E. Activation of protein kinase r is required for induction of stress granules by respiratory syncytial virus but dispensable for viral replication. *Virology* **2011**, *413*, 103-110.
106. Yang, X.D., Hu, Z. L., Fan, S. S., Zhang, Q., Zhong, Y., Guo, D., et al. Picornavirus 2a protease regulates stress granule formation to facilitate viral translation. *PLoS Pathog* **2018**, *14*, e1006901.
107. Simpson-Holley, M., Kedersha, N., Dower, K., Rubins, K. H., Anderson, P., Hensley, L. E., et al. Formation of antiviral cytoplasmic granules during orthopoxvirus infection. *J Virol* **2011**, *85*, 1581-1593.
108. Okonski, K.M.; Samuel, C.E. Stress granule formation induced by measles virus is protein kinase pkr dependent and impaired by rna adenosine deaminase adar1. *J Virol* **2013**, *87*, 756-766.
109. Heinicke, L.A.; Wong, C.J.; Lary, J.; Nallagatla, S.R.; Diegelman-Parente, A.; Zheng, X.; Cole, J.L.; Bevilacqua, P.C. Rna dimerization promotes pkr dimerization and activation. *J Mol Biol* **2009**, *390*, 319-338.
110. Takeuchi, K.; Komatsu, T.; Kitagawa, Y.; Sada, K.; Gotoh, B. Sendai virus c protein plays a role in restricting pkr activation by limiting the generation of intracellular double-stranded rna. *J Virol* **2008**, *82*, 10102-10110.
111. Venticinque, L.; Meruelo, D. Sindbis viral vector induced apoptosis requires translational inhibition and signaling through mcl-1 and bak. *Mol Cancer* **2010**, *9*, 37.
112. Smith, J.A.; Schmechel, S.C.; Raghavan, A.; Abelson, M.; Reilly, C.; Katze, M.G.; Kaufman, R.J.; Bohjanen, P.R.; Schiff, L.A. Reovirus induces and benefits from an integrated cellular stress response.

J Virol **2006**, *80*, 2019-2033.

113. Chan, S.W.; Egan, P.A. Hepatitis c virus envelope proteins regulate chop via induction of the unfolded protein response. *FASEB J* **2005**, *19*, 1510-1512.
114. Ruggieri, A.; Dazert, E.; Metz, P.; Hofmann, S.; Bergeest, J.P.; Mazur, J.; Bankhead, P.; Hiet, M.S.; Kallis, S.; Alvisi, G., *et al.* Dynamic oscillation of translation and stress granule formation mark the cellular response to virus infection. *Cell Host Microbe* **2012**, *12*, 71-85.
115. Montero, H.; Rojas, M.; Arias, C.F.; Lopez, S. Rotavirus infection induces the phosphorylation of eif2alpha but prevents the formation of stress granules. *J Virol* **2008**, *82*, 1496-1504.
116. Rojas, M.; Arias, C.F.; Lopez, S. Protein kinase r is responsible for the phosphorylation of eif2alpha in rotavirus infection. *J Virol* **2010**, *84*, 10457-10466.
117. Linero, F.N.; Thomas, M.G.; Boccaccio, G.L.; Scolaro, L.A. Junin virus infection impairs stress-granule formation in vero cells treated with arsenite via inhibition of eif2alpha phosphorylation. *J Gen Virol* **2011**, *92*, 2889-2899.
118. Qin, Q.S.; Hastings, C.; Miller, C.L. Mammalian orthoreovirus particles induce and are recruited into stress granules at early times postinfection. *J Virol* **2009**, *83*, 11090-11101.
119. Abrahamyan, L.G., Chatel-Chaix, L., Ajamian, L., Milev, M. P., Monette, A., Clement, J. F., et al. Novel staufen1 ribonucleoproteins prevent formation of stress granules but favour encapsidation of hiv-1 genomic rna. *J Cell Sci* **2010**, *123*, 369-383.
120. Raaben, M.; Groot Koerkamp, M.J.A.; Rottier, P.J.M.; de Haan, C.A.M. Mouse hepatitis coronavirus replication induces host translational shutoff and mrna decay, with concomitant formation of stress granules and processing bodies. *Cell Microbiol* **2007**, *9*, 2218-2229.
121. Poblete-Duran, N.; Prades-Perez, Y.; Vera-Otarola, J.; Soto-Rifo, R.; Valiente-Echeverria, F. Who regulates whom? An overview of rna granules and viral infections. *Viruses* **2016**, *8*, 180.
122. Fung, T.S.; Liao, Y.; Liu, D.X. The endoplasmic reticulum stress sensor ire1alpha protects cells from apoptosis induced by the coronavirus infectious bronchitis virus. *J Virol* **2014**, *88*, 12752-12764.
123. Wang, X.; Liao, Y.; Yap, P.L.; Png, K.J.; Tam, J.P.; Liu, D.X. Inhibition of protein kinase r activation and upregulation of gadd34 expression play a synergistic role in facilitating coronavirus replication by maintaining de novo protein synthesis in virus-infected cells. *J Virol* **2009**, *83*, 12462-12472.
124. Benali-Furet, N.L., Chami, M., Houel, L., De Giorgi, F., Vernejoul, F., Lagorce, D., et al. Hepatitis c virus core triggers apoptosis in liver cells by inducing er stress and er calcium depletion. *Oncogene* **2005**, *24*, 4921-4933.
125. Ciccaglione, A.R., Costantino, A.,Tritarelli, E., Marcantonio, C., Equestre, M., Marziliano, N., et al. Activation of endoplasmic reticulum stress response by hepatitis c virus proteins. *Arch Virol* **2005**, *150*, 1339-1356.
126. Ciccaglione, A.R., Marcantonio, C., Tritarelli, E., Equestre, M., Vendittelli, F., Costantino, A., et al. Activation of the er stress gene gadd153 by hepatitis c virus sensitizes cells to oxidant injury. *Virus Res* **2007**, *126*, 128-138.
127. Su, H.L.; Liao, C.L.; Lin, Y.L. Japanese encephalitis virus infection initiates endoplasmic reticulum stress and an unfolded protein response. *J Virol* **2002**, *76*, 4162-4171.
128. Umareddy, I.; Pluquet, O.; Wang, Q.Y.; Vasudevan, S.G.; Chevet, E.; Gu, F. Dengue virus serotype infection specifies the activation of the unfolded protein response. *Virol J* **2007**, *4*, 91.
129. Li, Y.R., Jiang, W. Y., Niu, Q. N., Sun, Y. J., Meng, C. C., Tan, L., et al. Eif2α-chop-bcl-2/jnk and ire1α-xbp1/jnk signaling promote apoptosis and inflammation and support the proliferation of newcastle

disease virus. *Cell Death & Disease* **2019**, *10*, 891.

130. Ma, Y.; Wang, C.; Xue, M.; Fu, F.; Zhang, X.; Li, L.; Yin, L.; Xu, W.; Feng, L.; Liu, P. The coronavirus transmissible gastroenteritis virus evades the type i interferon response through ire1alpha-mediated manipulation of the microrna mir-30a-5p/socs1/3 axis. *J Virol* **2018**, *92*.
131. Albornoz, A.; Carletti, T.; Corazza, G.; Marcello, A. The stress granule component tia-1 binds tick-borne encephalitis virus rna and is recruited to perinuclear sites of viral replication to inhibit viral translation. *J Virol* **2014**, *88*, 6611-6622.
132. Rathore, A.P.S., Ng, M. L., and Vasudevan, S.G. Differential unfolded protein response during chikungunya and sindbis virus infection chikv nsp4 suppresses eif2α phosphorylation. *Virology Journal* **2013**, *10*, 36.
133. Redondo, N.; Sanz, M.A.; Welnowska, E.; Carrasco, L. Translation without eif2 promoted by poliovirus 2a protease. *PLoS One* **2011**, *6*, e25699.
134. de Breyne, S.; Bonderoff, J.M.; Chumakov, K.M.; Lloyd, R.E.; Hellen, C.U. Cleavage of eukaryotic initiation factor eif5b by enterovirus 3c proteases. *Virology* **2008**, *378*, 118-122.
135. Chiramel, A.I.; Brady, N.R.; Bartenschlager, R. Divergent roles of autophagy in virus infection. *Cells* **2013**, *2*, 83-104.
136. Zhou, D.; Palam, L.R.; Jiang, L.; Narasimhan, J.; Staschke, K.A.; Wek, R.C. Phosphorylation of eif2 directs atf5 translational control in response to diverse stress conditions. *J Biol Chem* **2008**, *283*, 7064-7073.
137. Melber, A.; Haynes, C.M. Upr(mt) regulation and output: A stress response mediated by mitochondrial-nuclear communication. *Cell Res* **2018**, *28*, 281-295.
138. Quiros, P.M.; Prado, M.A.; Zamboni, N.; D'Amico, D.; Williams, R.W.; Finley, D.; Gygi, S.P.; Auwerx, J. Multi-omics analysis identifies atf4 as a key regulator of the mitochondrial stress response in mammals. *J Cell Biol* **2017**, *216*, 2027-2045.
139. Fiorese, C.J.; Schulz, A.M.; Lin, Y.F.; Rosin, N.; Pellegrino, M.W.; Haynes, C.M. The transcription factor atf5 mediates a mammalian mitochondrial upr. *Curr Biol* **2016**, *26*, 2037-2043.