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# Endoplasmic Reticulum Stress and Viral Infections

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***Abstract:*** *Endoplasmic reticulum is responsible for protein and lipid synthesis, processing and maturation within the cell. When a virus infects a cell, it also uses the endoplasmic reticulum to complete the protein synthesis of the virus itself. At the same time, the accumulation of large amounts of viral proteins induces stress responses in the endoplasmic reticulum, which then regulates various signalling pathways to maintain cellular homeostasis, leading to autophagy, apoptosis and metabolic syndrome. Some viruses enhance their own replication by altering the expression of proteins in stress pathways that are detrimental to their replication, at the same time maintaining aspects that are beneficial to them. In this paper, we provide a brief review of endoplasmic reticulum stress and unfolded protein response signalling pathways and the interactions between some viral infections and endoplasmic reticulum stress and some metabolic syndromes caused by viral infections and summarize the latest findings on endoplasmic reticulum stress and viral infections with the aim of providing ideas for endoplasmic reticulum stress-related antiviral infections research.*

***Keywords:*** *Endoplasmic Reticulum Stress, Viral Infection, Unfolded Protein Response, Metabolic Syndrome*

## 1. Introduction

Endoplasmic reticulum (ER) is an important membranous reticular organelle, mainly responsible for protein synthesis, folding, modification, secretion and transport, and is a key organelle for translation and maturation of viral proteins. When exogenous pathogens invade cells for replication and proliferation, their structural and non-structural proteins are expressed in large quantities, which destroys the balance of the endoplasmic reticulum, leading to the rapid accumulation of misfolded and unfolded proteins in the endoplasmic reticulum and a sudden change in the level of calcium ions, ultimately the endoplasmic reticulum faces great pressure, which puts the cell in a state of stress named as endoplasmic reticulum stress (ERS) [1]. Autophagy, apoptosis and even the metabolism are all closely related to endoplasmic reticulum stress. The study of endoplasmic reticulum stress is of great significance for the treatment of viral infections and related metabolic syndromes.

STING proteins are mainly expressed on the rough endoplasmic reticulum, mitochondria and outer membrane of microsomes in human macrophages, T lymphocytes, dendritic cells, endothelial cells, epithelial cells and fibroblasts [4]. As a central immune molecule in many signalling pathways, STING is usually in a self-inhibited state in the form of a dimer, which is activated by a change in protein conformation after stimulation by upstream signals, and then causes the activation and production of a series of downstream immune cells and inflammatory factors, thus promoting the occurrence of inflammatory reactions in the body and producing corresponding clinical symptoms. The role of STING, related signalling pathways and its role in inflammatory diseases is now reviewed.

## 2. UPR Signalling Pathways

The unfolded protein response (UPR) is a cellular adaptive response to restore endoplasmic reticulum homeostasis in response to endoplasmic reticulum stress. It promotes protein folding, inhibits protein synthesis, enhances endoplasmic reticulum-associated degradation (ERAD), and eliminates misfolded and unfolded proteins by up-regulating the molecular chaperone, immunoglobulin heavy chain (BIP)-

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binding proteins [1-2].

BIP, also known as glucose-regulated protein 78 (GRP78), is a member of the heat shock family of proteins. BIP is a signature molecule of the UPR response, and binds to and inhibits three proximal UPR sensors in the resting state: activating transcription factor 6 (ATF6), RNA-dependent protein kinase-like E R-resident kinase (PERK) and type I ER transmembrane protein kinase (IRE1) [3-4].

When unfolded and misfolded proteins accumulate in the endoplasmic reticulum, BIP is segregated by misfolded or unfolded proteins, disconnecting from the UPR sensors and activating the three response pathways accordingly [4]. BIP not only serves as a chaperone protein to facilitate folding or assembly of proteins, but also serves as a sensing molecule for the detection of unfolded or misfolded viral proteins at the initial stage of the stress response [5].

### *2.1 ATF6* Signalling Pathway

ATF6, a member of the ATF/cAMP family of basic leucine zip protein binding proteins, is a type II endoplasmic reticulum transmembrane protein with its NH2-terminal DNA-binding domain oriented towards the cytoplasm and its COOH-terminal end located in the lumen of the endoplasmic reticulum. ATF6 is disconnected from BIP and translocated to the Golgi apparatus to be cleaved into an active transcription factor by the ite-1 and ite-2 proteases to form active transcription factors. The amino acid terminal domains released by protease hydrolysis translocate to the nucleus and induce the expression of genes encoding proteins or folding enzymes, such as BIP, glucose-regulated protein 94 and P58IPK. It is noteworthy that the terminal molecule of the ATF6 pathway, P58IPK, is an inhibitor of PERK, so the ATF6 pathway is often studied in conjunction with the PERK pathway [6].

### *2.2 PERK-eIF2α-ATF4 Signalling Pathway*

Accumulation of unfolded or misfolded proteins activates the PERK pathway, which is phosphorylated at serine 51 [7], followed by phosphorylation of eIF2α by phosphorylated PERK, and phosphorylation of eIF2α induces the expression of activating transcription factor 4 (ATF4), a transcription factor that stimulates the expression of C/E homologous protein (CHOP), growth arrest, and DNA damage-inducible protein 34 and also increases protein secretion to promote cell survival [9].

CHOP, also known as growth arrest and DNA damage inducible protein 153 (GADD153), is a dominant negative repressor of CCAAT/enhancer binding proteins. When expressed in mammalian cells, CHOP/GADD153 promotes apoptosis [10 -11].

Gadd34 is expressed under conditions, such as DNA damage and growth arrest. It has been shown that Gadd34 is a regulatory subunit of protein phosphatase 1, which is recruited via the carboxy-terminal end of protein phosphatase 1. The recruited protein phosphatase 1 dephosphorylates eIF2α and negatively regulates the PERK pathway, alleviating translational repression by endoplasmic reticulum stress and gene expression under stress conditions [9, 12].

### *2.3 IRE1-XBP1 Signalling Pathway*

IRE1 is a protein that contains an ER hydroxyamino-terminal structural domain, a transmembrane region, a serine/threonine kinase structural domain and a carboxy-terminal nucleic acid endonuclease structural domain in the cytoplasm. When excess misfolded proteins accumulate in the endoplasmic reticulum, the release and dimerisation and cross-phosphorylation of the IRE1 monomer bound to GRP78 and activates the activity of IRE1 as a nucleic acid endonuclease that cleaves and removes the 26-nucleotide intron from the XBP -1 mRNA to form the shifted transcript spliced with XBP - 1 ( XBP-1s) [13]. Unspliced XBP-1 (XBP-1u) mRNA encodes a repressor of the UPR. XBPIs transcription factors activate target genes such as α-glycoside-like protein (EDEM) that promotes ER degradation, which promotes the degradation of misfolded proteins [14].

## 3. Links between Endoplasmic Reticulum Stress, Autophagy and Apoptosis

Autophagy is a major cellular catabolic process that transports proteins, cytoplasmic components, and organelle fragments to lysosomes for degradation cycles. Currently, more than 30 autophagy-related genes (ATGs) have been identified to carefully encode the autophagy programme [15 -16]. It has been demonstrated that PERK - eIF2α plays a key role in autophagy induction in endoplasmic reticulum stress,

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and that ATF4 and CHOP, signalling molecules downstream of the PERK pathway, upregulate more than 12 ATG genes during transcription [17].

In the IRE1 pathway, activation of tumor necrosis factor receptor-associated factor 2 (TRAF2) and c-Jun amino-terminal kinase (JNK) leads to the phosphorylation of Bcl-2, which dissociates Beclin-1 (an autophagy-regulating protein) and activates phosphatidylinositol-3-kinase (PI3K) complex and autophagy [15].

Under endoplasmic reticulum stress, the ERAD produced is mainly through the ubiquitin-protease system (UPS) to degrade ubiquitinated unfolded or misfolded proteins. Autophagy is also an atypical ERAD pathway [18-19]. Some misfolded proteins that cannot be degraded by typical ERAD mechanisms due to the formation of aggregates or some special structures can be efficiently degraded and removed by autophagy. For example, mutant A1-antitrypsin or misfolded gonadotropin-releasing hormone receptor (GnRHR) [20 -21].

Another cellular physiological activity that is closely linked to the endoplasmic reticulum is apoptosis, the genetically controlled programmed death of cells in order to maintain the stability of the internal environment. Apoptosis is an active process chosen by cells to be able to better adapt to their environment in the face of internal environmental dysregulation. During apoptosis, the cysteine protease family plays an important role. Apoptosis is activated by recruitment of the death-inducing stimulatory complex (DISC) via Caspase-8, a member of the cysteine protease family [22 -23] or via Caspse -9, which mediates apoptotic signalling after mitochondrial injury [24]. The UPR responses can also regulate apoptosis when endoplasmic reticulum stress is prolonged in a highly stressful state and cannot be relieved. Therefore, endoplasmic reticulum stress is also considered to be another regulatory centre of cell death [25]. IRE1 recruits TRAF2 and in turn recruits ASK, a proximal component of the activation of the c-Jun N-terminal kinase (JNK) pathway [26]. Prolonged activation of ASK and JNK leads to apoptosis [27]. Another pathway by which the endoplasmic reticulum regulates apoptosis is the induction of cytochrome release from mitochondria and the activation of the caspase-8 pathway. Bcl-2/CB5 protein is an endoplasmic reticulum-targeted Bcl-2 protein that inhibits endoplasmic reticulum stress-mediated cytochrome c release [28]. RNT-Xs, a family of lattice proteins, interacts with Bcl-2 through the endoplasmic reticulum and reduces the anti-apoptotic activity of Bcl-2 and Bcl-XL in clostridium-induced cell death [29].

## 4. Endoplasmic Reticulum Stress and Viral Infections

During infection, viruses synthesize large amounts of viral proteins, putting the endoplasmic reticulum under stress. In order to maintain its homeostasis, cell will often activate the UPR-mediated protein degradation pathway (ERAD) and host cell apoptosis, autophagy and other regulatory mechanisms to inhibit or degrade the synthesis and accumulation of viral proteins. At the same time, the virus will provide a suitable environment for its replication and proliferation in the host through counter-regulation or utilization of the UPR response, and ultimately leading to successful replication. The sustained UPR and inflammatory response caused by viral infection may also be an important etiological factor in viral diseases. During the endoplasmic reticulum stress induced by viruses, they may specifically regulate a particular pathway in the UPR response to favor viral replication or they may regulate cellular autophagy induced by endoplasmic reticulum stress to alleviate the pressure on the cell itself and prevent apoptosis, ultimately to sustain the infection.

### *4.1 RNA Viruses*

#### *4.1.1 Dengue Virus (DENV)*

DENV induces different UPR pathways at different times of viral infection: activating the PERK pathway in early infection, the IRE1 pathway in mid-infection, and the ATF6 pathway in late infection [30]. Viral replication is inhibited by the weakening of protein translation through the early PERK pathway, which is then rapidly reversed by the virus to ensure the level of protein translation for smooth assembly of viral particles [30-31]. Activation of the IRE1 pathway in the mid-phase and activation of XBP-1 target genes such as EDEM facilitates the degradation of some proteins to relieve endoplasmic reticulum stress and protect cells from apoptosis, favoring persistent viral infection [32]. Activation of the XBP-1 pathway is induced by the ER-associated DENV glycoproteins (PRM, E, and NS1) and smaller hydrophobic ER-anchored viral proteins (NS2A, NS2B, and NS4B) and DENV inhibits apoptotic genes downstream of the pathway, which improves cell survival and facilitates viral infection. DENV-mediated endoplasmic reticulum stress and the UPR activate autophagy [33] and the PERK pathway up-regulates reactive oxygen

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species (ROS), which are important in maintaining a high level of autophagy. During infection, the PERK pathway upregulates reactive oxygen species (ROS), which are important for maintaining high autophagy levels, and facilitates the production of mature and infectious viral particles [33]. During the activation of autophagy, the double membrane vesicles formed provide a platform for viral replication [34], which ultimately increases the viral load inside and outside the cell, and at the same time promotes the β-oxidation of cellular lipids, which provides adenosine triphosphate (ATP) for the virus [35].

#### *4.1.2 Hepatitis C Virus (HCV)*

HCV genome encodes 2 envelope proteins, E1 and E2, which mature in the endoplasmic reticulum to form non-covalently bonded natural complexes and disulfide-bonded aggregates. The non-structural proteins of the virus form a ribonucleoprotein complex on the reticular ER membrane in the perinuclear region [36], which plays a key role in the replication of the viral genome and the establishment of infection in hepatocytes. This viral protein puts great pressure on the endoplasmic reticulum, inducing endoplasmic reticulum stress and subsequently causing the unfolded protein response [37]. In the UPR response induced by HCV, the level of ATF6 cleavage is markedly increased, which induces GRP78, a hallmark molecule of the UPR. In the PERK pathway of UPR, viruses inhibit the phosphorylation of eIF2α, blocking the translational inhibition of this pathway and allowing the normal expression of viral proteins [38]. HCV replication alters the typical features of the UPR signalling pathway and prolong viral survival, thus facilitating the proliferation of the virus itself [37].

#### *4.1.3 Porcine Epidemic Diarrhoea Virus (PEDV)*

The structural proteins S and M of PEDV, as well as the non-structural protein ORF3, induce endoplasmic reticulum stress and elevated BIP [39]. These proteins mainly activate the PERK pathway in the UPR signalling pathway, resulting in a significant increase in the phosphorylation levels of PERK and eIF2α. The virus had no significant effect on ATF6 protease cleavage and XBP-1 transcriptional cleavage in the IRE1 pathway. PEDV further stimulates autophagy by inducing endoplasmic reticulum stress, leading to cell death. In PEDV-infected cells, treatment with Salubrinal, a drug that specifically enhances the activation of the PERK signalling pathway, inhibited viral replication [40], suggesting that the endoplasmic reticulum inhibits viral infection via the PERK pathway. Whether PEDV is resistant to the inhibitory effect of UPR requires more in-depth study.

### *4.2 DNA Viruses*

#### *4.2.1 Hepatitis B Virus (HBV)*

HBV can induce endoplasmic reticulum stress and activate the IRE1- XBP -1 pathway of the unfolded protein response (UPR) through the expression of viral regulatory protein X (HBx). Available studies have shown that the hepatitis B virus surface antigen HBSAG is the main cause of endoplasmic reticulum stress induced by HBV [41].The target gene of XBP-1, EDEM, is tightly linked to the life cycle of HBV, and interestingly, the virus does not inhibit the transcription of its target gene, but stimulates the endoplasmic reticulum-associated degradation (ERAD) pathway to up-regulate the up-regulation of the relevant degradation factors such as EDEM1, EDEM2 and other related degradation genes [42]. This reduces the number of envelope proteins, decreases endoplasmic reticulum stress, and inhibits apoptosis due to prolonged endoplasmic reticulum stress, thereby promoting viral proliferation and establishing persistent infection. In HBV-infected mice, the phenomenon of ground glass hepatocytes (GGH) has been identified, which is caused by an excess of surface antigens in the endoplasmic reticulum, resulting in a uniformly dark cytoplasm and ultimately a glassy appearance [43]. Chronic HBV is strongly associated with hepatocellular carcinoma cells, and GGH has been shown to be a marker for hepatocellular carcinoma; these clues may suggest that hepatocellular carcinoma cells induced by HBV are somehow intrinsically linked to endoplasmic reticulum stress.

#### *4.2.2 Human Cytomegalovirus (HCMV)*

HCMV induces ERS, which regulates three UPR response pathways to facilitate self-replication. HCMV induces phosphorylation of PERK and eIF2α and it has been shown that phosphorylated eIF2α does not cause translational inhibition in HCMV-infected cells. In the ATF6 pathway, HCMV induces ATF6 glycosylation and translocation to the Golgi, but inhibits its shearing in the Golgi, which in turn inhibits the transcriptional activity of ATF6, resulting in the blockage of downstream BIP or GRP94 expression. In the IRE1 pathway, HCMV infection stimulates splicing of XBP-1 mRNA, however, the XBP-1 target gene EDEM was not detected in HCMV-infected cells, and the expression of proteins such as EDEM inhibits viral replication, which triggers the UPR response by inhibiting such proteins to create

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conditions favorable for self-replication [44]. By inhibiting these proteins, the virus triggers the UPR response, thus creating conditions favorable to its own replication [45]. During HCMV infection, the viral US12 family gene encodes an ion channel viral protein US12, which reduces the accumulation of $Ca^{2+}$ in the endoplasmic reticulum of cells, relieves endoplasmic reticulum stress and saves cells from apoptosis caused by persistent endoplasmic reticulum stress, thus promoting cell survival and prolonging the time of viral replication [45]. In conclusion, during HCMV infection, the UPR is induced but modified in a manner that favors viral infection, inhibits unfavorable effects on viral replication and maintains favorable effects.

#### *4.2.3 Pseudorabies Virus (PRV)*

Increased expression of BIP induced endoplasmic reticulum stress during the early stages of PRV infection. BIP was up-regulated during the early stages of infection in PK-15 cells, enhancing protein folding in the endoplasmic reticulum in favor of viral infection. Subsequently, BIP expression was inhibited to avoid severe endoplasmic reticulum stress, which led to apoptosis and prevented the continuation of viral infection. Detection of the three branches of the UPR showed that the IRE1- XBP-1 pathway was activated during PRV infection, but inhibition of the expression of this pathway had no significant effect on viral replication, and the inherent complex mechanism has not been well explained [46].

#### *4.2.4 Porcine Circovirus Type 2 (PCV2)*

PCV2 ORF5 protein is localized in the endoplasmic reticulum and induces endoplasmic reticulum stress by inducing dilatation and swelling of the endoplasmic reticulum lumen and upregulating the protein levels of the stress marker molecules BIP and GRP94 [47]. Available studies have shown that PCV2 activates the PERK pathway and selectively activates the downstream factors of the pathway, and the replication of PCV2 was also significantly inhibited after inhibiting the dephosphorylation of eIF2α with danshenin. After the dephosphorylation of eIF2α was inhibited by danshenin, the replication of PCV2 was also significantly inhibited. Therefore, PCV2 may restore the cellular translation level through the dephosphorylation of eIF2α, enhance the expression of viral proteins, and favor its own replication [48]. Taurine ursodeoxycholic acid (TUDCA) itself can alleviate endoplasmic reticulum stress by strengthening protein folding, and PCV2 replication was significantly enhanced after treatment of cells with TUDCA [49]. TUDCA cooperates with the folding and assembly of PCV2 capsid proteins, and its anti-apoptotic effect also provides a favorable site for PCV2 infection.

## 5. Endoplasmic Reticulum Stress and Metabolic Syndrome due to Viral Infection

In the physiological activities of cells, the endoplasmic reticulum not only serves as a site for protein folding, processing and secretion, but also plays a key role in lipid and glucose metabolism and the sensing and signalling mechanisms of many metabolic channels are present in the endoplasmic reticulum membrane or structural domains [50]. For example, SREBPs, a key factor responsible for regulating lipid metabolism, are attached to the endoplasmic reticulum membrane in the normal state when the body's lipid level is low, they are translocated to the Golgi apparatus and activated by protease hydrolysis and cleavage, and are transferred to the nucleus to regulate lipid genes, and the endoplasmic reticulum initiates cholesterol synthesis through this pathway [51]. Through this pathway, endoplasmic reticulum stress is closely associated with a variety of viral hepatitis. Disturbances in lipid metabolism are also induced in chronic endoplasmic reticulum stress induced by various hepatotropic viruses.

There is now growing evidence that endoplasmic reticulum stress is also linked to both diabetes and atherosclerosis. In the normal state, activated insulin receptors phosphorylate proximal signalling molecules on tyrosine residues, also known as insulin receptor substrates (IRS-1), which interact with cytoplasmic targets to exert insulin function. This phosphorylation is inhibited by the JNK-associated IRS-1 serine phosphorylation pathway in the presence of obesity, genetics and poor diet [52] and the mechanism of JNK activation associated with obesity is related to endoplasmic reticulum stress. Endoplasmic reticulum stress directly triggers the JNK cascade through the IRE1 pathway [26]. Through activation of the JNK family, the endoplasmic reticulum is involved in the lipotoxic pathway, which in turn induces the metabolic syndrome, characteriZed by glucose tolerance and insulin resistance [53].

## 6. Conclusions

The endoplasmic reticulum stress generated by the cell belongs to its own mechanism of adaptation

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to the environment, with different pathways to address various endoplasmic reticulum stresses caused by the external environment, with the aim of increasing the probability of cell survival. When this stress further undermines the overall survival interest of the organism, the cell will adopt autophagy or apoptosis to maintain the homeostasis of the organism.

Endoplasmic reticulum stress occurs when virus invades host cells, translates and synthesises large amounts of viral proteins, accumulates in the endoplasmic reticulum, or causes an imbalance of endoplasmic reticulum $Ca^{2+}$. The antagonistic responses of different viruses to endoplasmic reticulum stress are different. On the one hand, some viruses can control endoplasmic reticulum stress, induce UPR to facilitate viral protein folding and viral replication, or enable viruses to sustain infection through autophagy [54]. On the other hand, the consequences of the UPR, such as attenuation of translation, ERAD and apoptosis, limit viral replication [46]. Different viruses have different strategies in counteracting the UPR response. Herpes simplex virus type 1 (HSV-1) triggers PERK activation and mediates eIF2α dephosphorylation [55]. Glycoprotein B (gB) of HSV-1 regulates the accumulation of viral proteins by associating with PERK in order to maintain endoplasmic reticulum homeostasis. HSV-1 was found to be effective in disarming the UPR early in viral infection and activating the eIF2α-ATF4 signalling pathway during the final stages of viral replication. However, tick-borne encephalitis virus (TBEV) triggers the IRE1 pathway of the UPR and ATF6, and an IRE1 inhibitor (3,5-dibromosalicylaldehyde) significantly limits TBEV replication in Vero E6 cells.

Study of endoplasmic reticulum stress is not only important for understanding the complex mechanisms of viral infection of cells, but also for combating and exploiting viruses in the present time. In the case of TBEV described above, the use of UPR inhibitors could be a novel therapeutic strategy to combat viral infection. In the study of HIV protease inhibitors, although the drugs themselves may improve the quality of life of AIDS patients, they may also cause lipid dysregulation and atherosclerosis, the key reason being the activation of endoplasmic reticulum stress by the drugs themselves.

The in-depth study of endoplasmic reticulum stress and the subsequent UPR in close conjunction with cellular autophagy, apoptosis, and metabolic processes enables a more in-depth and thorough study of viruses, and also provides a completely new direction for the study of viruses and some complex physiological features. In the process of fighting viruses, various factors in the UPR reaction may also be effective targets for inhibiting viral replication, and the development of new drugs or vaccines against these targets is of great significance in reducing the damage of viruses to humans or animals.

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