Modulation of Endoplasmic Reticulum Stress Response Pathways by Respiratory Viruses

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Abstract

Acute respiratory infections (ARIs) are amongst the leading causes of death and disability, and the greatest burden of disease impacts children, pregnant women, and the elderly. Respiratory viruses account for the majority of ARIs. The unfolded protein response (UPR) is a host homeostatic defence mechanism primarily activated in response to aberrant endoplasmic reticulum (ER) resident protein accumulation in cell stresses including viral infection. The UPR has been implicated in the pathogenesis of several respiratory diseases, as the respiratory system is particularly vulnerable to chronic and acute activation of the ER stress response pathway. Many respiratory viruses therefore employ strategies to modulate the UPR during infection, with varying effects on the host and the pathogens. Here, we review the specific means by which respiratory viruses affect the host UPR, particularly in association with the high production of viral glycoproteins, and the impact of UPR activation and subversion on viral replication and disease pathogenesis. We further review the activation of UPR in common co-morbidities of ARIs and discuss the therapeutic potential of modulating the UPR in virally induced respiratory diseases.

Keywords

Respiratory virus infection; virus-host biology; unfolded protein response; glycoproteins; viral replication; influenza virus; respiratory syncytial virus; coronavirus

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Introduction to Respiratory Viruses

Viruses account for the vast majority of acute respiratory infections (ARIs) [1, 2]. Hundreds of viruses serve as potential aetiologic agents in ARIs, although the majority of human infections occur largely as a result of a select few groups [3].

Human rhinoviruses (RV) are the principal cause of the common cold, and account for the majority of upper respiratory infections in children under 5 years [4, 5]. The second most prevalent viruses responsible for the common cold are the seasonal human coronaviruses (CoV): HKU1, OC43, NL63 and 229E [5]. Beyond those that cause relatively mild disease, three CoV strains have been responsible for severe disease outbreaks in humans: Severe Acute Respiratory Syndrome (SARS) by SARS-CoV-1, Middle East Respiratory Syndrome (MERS) by MERS-CoV, and most recently Coronavirus Disease 2019 (COVID-19) by SARS-CoV-2 [6]. Another agent typically associated with mild respiratory infections are adenoviruses (AdV), although they can also cause severe respiratory illness [3].

Influenza viruses, most notably the influenza A virus (IAV), are responsible for seasonal and pandemic outbreaks of influenza, a respiratory disease which disproportionately burdens the elderly [7, 8]. The Paramyxoviridae family of viruses account for another large proportion of ARIs, and includes respiratory syncytial virus (RSV), parainfluenza virus (PIV) and human metapneumovirus (HMPV). RSV infections burden elderly populations and are also especially frequent amongst children under 5; in individuals younger than 6 months they represent the leading cause of lower respiratory infections [9, 10]. Hospitalisations due to HMPV and PIV infection are most common in children from 6 to 12 months, but infections are also strongly associated with the

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elderly and immune compromised [3]. Collectively, these viruses represent the major viral antagonists to the respiratory system; understanding the diverse ways these viruses interact with their hosts is critical in reducing the burden of respiratory disease caused by ARIs. However, as the majority of research into respiratory viruses focuses on IAV, CoVs and RSV, it is these viruses that are the principle focus of this review.

Viral Replication Cycle

As obligate intracellular pathogens, viruses must enter the host cell to exploit host machinery [11]. To gain entry to the host cell, a critical first step in any virus replication cycle is attachment to the host cell's surface, which in many respiratory viruses is mediated by viral surface glycoproteins [12]. Viral entry strategies can broadly be classified as occurring through direct fusion or receptor-mediated endocytosis, with viral surface glycoproteins playing a critical role in both [13, 14]. The next stage of viral replication is expression of the viral genome and the generation of new viral particles through the exploitation of host translation machinery. This includes the biosynthetic secretory pathway through the endoplasmic reticulum (ER) where proteins can undergo glycoylation [15].

Protein glycosylation is a post-translational modification involving the enzymatic attachment of complex sugars (glycans). Viral surface proteins are processed in the ER and acquire *N*-glycosylation, a form of glycosylation that occurs at the amide nitrogen of asparagine residues primarily located in N-X-S/T (X ≠ proline) consensus sequons [16, 17]. Glycosylation is a fundamental process critical for protein folding and function, including the receptor binding and fusion activities of viral surface proteins [18-21]. Critically, the high density of glycosylation sites

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on viral surface exposed glycoproteins can shield antigenic sites and help these viruses avoid host immunorecognition [21, 22]. Protein glycosylation in the ER is also critical in assisting productive protein folding by helping to recruit a variety of chaperones that catalyse protein folding and the formation of protein disulfide bonds. Protein chaperones such as the binding immunoglobulin protein (BiP), lectin chaperones calnexin and calreticulin, and protein disulfide isomerases act in concert to assist productive protein folding [23].

The final stages of the viral replication cycle are the assembly and exit of new viral particles from the cell. For non-enveloped viruses, release can be achieved through the lysis of cellular membranes. Enveloped viruses need to first be surrounded by a lipid bilayer prior to their extracellular release, typically by exocytosis or budding [24]. Some viruses, such as IAV, use the plasma membrane for envelopment [24]. Other viruses, including the CoVs, subvert ER membrane components for the formation of their own membranes [25].

Collectively, the processes associated with active viral infection typically lead to substantial stresses and changes to the status of the ER, and host cells sense these changes to trigger anti-viral responses. In particular, viral infection often causes biosynthesis of large amounts of viral proteins that can overwhelm the folding capacity of the ER and trigger the unfolded protein response (UPR) [26].

The Unfolded Protein Response

The UPR refers to a group of signalling pathways that collectively respond to the accumulation of aberrantly folded proteins, or other stresses otherwise incurred by the ER. As these stresses are

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common in viral infections, the UPR is a central anti-viral response pathway. The purpose of the UPR is to restore ER homeostasis in the event of disruption to protein synthesis, secretion, or degradation. UPR dysregulation is a hallmark of multiple pathologies, including neurodegenerative and fibrotic diseases [27]. ER stress is also a critical factor in the pathogenesis of many respiratory diseases [28].

The ER can experience stress in a variety of ways, but a central canonical feature of ER stress is the accumulation of misfolded proteins that have overwhelmed the protein-folding capacity of the ER [29]. Genes activated by the UPR largely serve to counteract this ER stress through regulation of protein glycosylation, lipid biogenesis, ER chaperones, ER-associated degradation (ERAD), and protein trafficking to the ER [30, 31]. As a result of UPR activation, increased expression of chaperones and ER expansion increases both the ER folding capacity and volume, while degradation of ER resident proteins and attenuation of protein translation reduces ER load to collectively restore ER homeostasis [32]. However, sustained or prolonged ER stress, indicating that homeostasis cannot be restored, shifts the pro-survival functions of the UPR towards pro-apoptotic functions [26].

The activation of the UPR is largely mediated by three innate stress sensors (Figure 1): inositol-requiring enzyme-1 (IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6) [33-35]. Under basal conditions, a ubiquitous inhibitor of UPR activation, BiP, binds these three sensors and maintains their inactivated conformation [36]. BiP’s main function is as a chaperone to promote the productive folding of nascent polypeptides as they enter the ER. Under conditions of ER stress, with increased intralumenal concentrations of misfolded proteins in the

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ER, BiP preferentially binds to the exposed hydrophobic residues of these misfolded proteins, thereby allowing the three UPR sensors to activate and affect their downstream pathways to restore ER homeostasis [37, 38]. It has also been suggested that in addition to the dissociation of BiP from the UPR sensors, direct interactions between unfolded proteins and the UPR sensors are required as a second regulatory step in this process [39]. Partial activation of the UPR could then be attributed to direct interactions of unfolded proteins with UPR sensors, or as a result of selective activation of the stress sensor(s) with the weakest affinity for BiP that are activated under low stress [40].

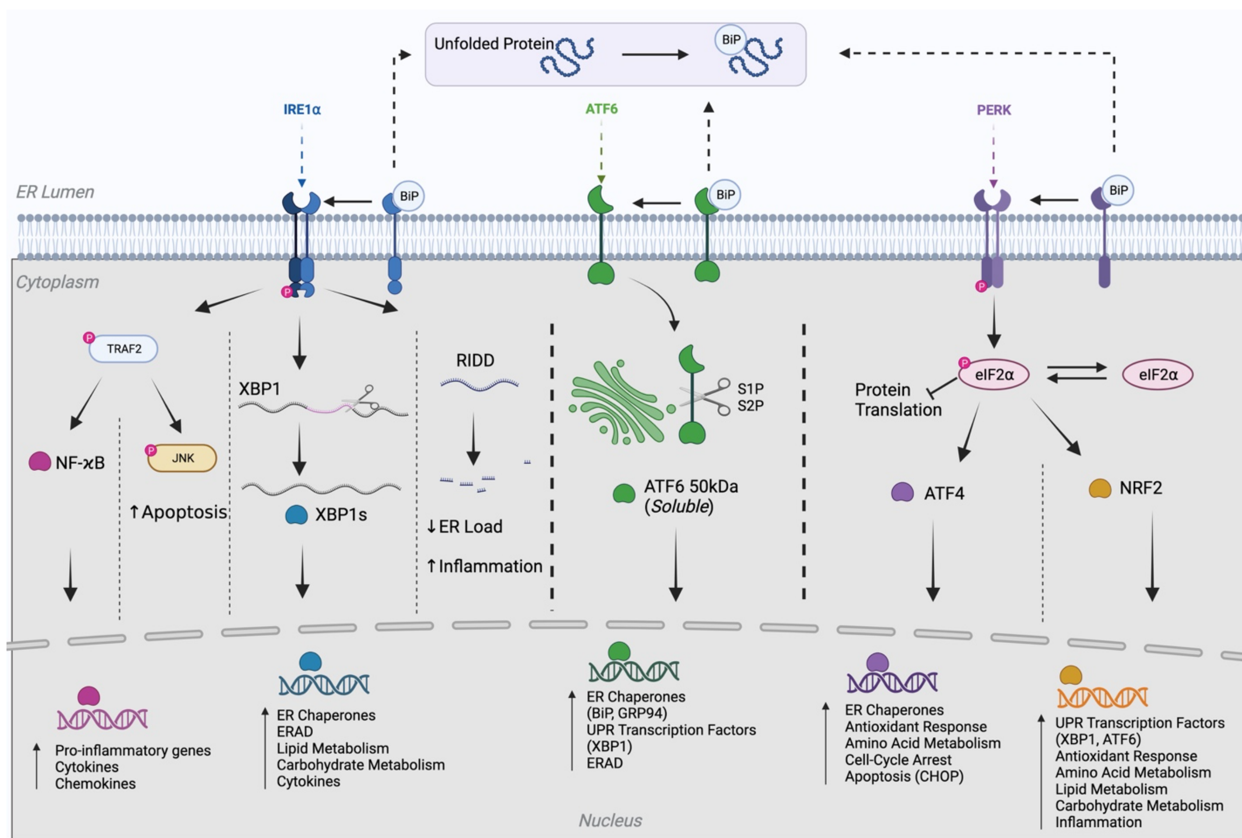

Figure 1. **The signalling pathways of the UPR.** Sequestration of BiP to hydrophobic regions of unfolded / misfolded proteins in the endoplasmic reticulum (ER) triggers the dimerization, phosphorylation and activation of IRE1 and PERK, and the translocation, proteolysis and activation of ATF6. The kinase activity of IRE1 is associated with

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TRAF2 phosphorylation and subsequent activation of NF-ϰB and JNK signalling pathways. The endoribonuclease activity of IRE1 is associated with splicing of a 26 nt transcript from XBP1 mRNA, and regulated IRE1-dependent decay (RIDD) of select ER-targeted mRNA. ATF6 is proteolytically cleaved by site proteases 1 and 2 (S1P/S2P) within the Golgi membrane, to produce a 50kDa soluble transcription factor. Active PERK phosphorylates eIF2α, which selectively inhibits ER protein translation, whilst promoting translation of transcription factors ATF4 and NRF2. General ER stress responses associated with each transcription factor are indicated below. Abbreviations: ATF: activated transcription factor, BiP: binding immunoglobulin protein, CHOP: C/EBP homologous protein, eIF2α: eukaryotic initiation factor 2α, ERAD: ER-associated degradation, GRP94: glucose-regulated protein 94, IRE1: inositol-requiring enzyme 1, NRF2: nuclear factor erythroid 2-related factor 2, PERK: PKR-like enzyme kinase, XBP1: x-box binding protein 1. Created with BioRender.com.

IRE1

The IRE1 arm of the UPR is the most evolutionarily conserved of all three pathways [41]. Two isoforms of IRE1 are present in mammals: the globally expressed IRE1α; and IRE1β, which is only expressed in goblet cells of the lung and the intestinal epithelium [42]. IRE1 has dual activity as a kinase and as an endoribonuclease [43, 44]. Once activated, IRE1 splices X-box binding protein 1 (XBP1) mRNA, producing a 26 nt spliced transcript (XBP1s), a potent transcription factor for genes containing either the ER stress response element (ERSE) or UPR element (UPRE) [45]. IRE1 also directly degrades ER targeted mRNA, thereby reducing the protein translational load of the ER in a process termed regulated IRE1-dependent decay (RIDD) [46]. IRE1 is further associated with nuclear factor-kappa β (NF-ϰβ) and Jun NH2-terminal kinase (JNK)-mediated signalling, and hence the signalling pathways of cytokine release and apoptosis [47, 48].

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ATF6

Dissociation of BiP from ATF6 results in exposure of two Golgi-localisation sequences on ATF6, and subsequently its translocation to the Golgi apparatus where it undergoes proteolysis by site-1 and site-2 proteases (S1P/S2P). This proteolysis produces a 50 kDa cytoplasmic fragment of ATF6, that is then translocated to the nucleus where it serves as a transcription factor for ER stress response genes bearing the ERSE [45]. Responses downstream of ATF6 activation include inducing expression of ER chaperones such as BiP and the glucose-regulated protein 94 (GRP94), UPR mediators such as XBP1, and components of the ERAD pathway.

PERK

The innate UPR sensor PERK is a member of the protein kinase family associated with the protein translation initiation complex. Activated PERK specifically phosphorylates the eukaryotic translation initiation factor 2α (eIF2α), which reduces the load on the ER by attenuating the translation of select mRNA [49]. This decrease to the ER protein translational load serves as the most immediate response to ER stress, as it is not reliant upon nuclear translocation of transcription factors, transcription, or translation [40]. Paradoxically, phosphorylated eIF2α promotes the translation of select mRNAs such as the activated transcription factor 4 (ATF4). PERK also directly phosphorylates nuclear factor erythroid 2-related factor 2 (NRF2), allowing its nuclear translocation where it functions as an additional transcription factor in conjunction with ATF4 [34].

UPR in Viral Respiratory Disease

Respiratory viruses employ several strategies to combat host immune responses, and the UPR is no exception [50-52]. Transcriptomic and proteomic profiling of the UPR in infection have

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revealed varied host ER stress responses. Infection with most common respiratory viruses results in increased expression of ER stress response genes and proteins [53-57], an observation that can be made directly in diseased patients [58]. Importantly, many respiratory viral infections elicit a non-canonical UPR by only activating a subset of the three UPR arms [51, 59-61]. For example, RSV and IAV infections induce preferential activation of IRE1 and ATF6, but not PERK, although IAV may also induce IRE1 alone or all three arms depending on infection conditions [59, 62]. UPR activation by respiratory viruses is likely somewhat cell-type specific. An example of this is observed in the atypical activation of PERK in RSV infected dendritic cells [63]. Non-canonical UPR activation strongly suggests that the UPR is specifically modulated by viruses. Of the numerous responses mediated by the UPR, some are generally detrimental to viral replication (i.e., viral protein translation inhibition, ERAD), whilst others may advantage the virus (i.e. ER expansion, chaperone expression). Rather unsurprisingly, there are therefore many mechanisms by which respiratory viruses are able to selectively induce or supress elements of the UPR [60]. These mechanisms include surface glycoproteins processed in high volume within the ER, viral ion channels, non-structural and accessory proteins, as well as various stress responses associated with infection.

Surface Glycoproteins

Flux of viral glycoproteins through the secretory pathway is a major contributor towards ER stress during infection [47]. BiP binds strongly with many surface glycoproteins of respiratory viruses that are often overexpressed and misfolded during infection [64]. As a key feature of these proteins, glycosylation, and variations in glycosylation site occupancies that may arise due to mutation, are

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important determinants of the folding efficiency of viral glycoproteins, and hence of UPR activation.

IAV

Two major surface glycoproteins are displayed by IAV, the haemagglutinin (HA) and neuraminidase (NA) proteins. HA is the more abundant glycoprotein; current influenza vaccines are designed to elicit antibody responses towards HA epitopes from strains of concern. HA binds to terminal sialic acid residues on the cell surface for attachment and has a further role in membrane fusion. Expression of HA in HEK293T cells is sufficient to induce the IRE1 signalling cascade [65]. Although HA is the principal factor inducing the UPR in IAV infection [65-67], NA is also associated with induction of all three sensors in human A549 cells [68]. The variable affinity of NA variants for BiP is a strong determinant of UPR activation in different IAV strains [53].

Glycosylation of HA and NA plays a major modulatory role in UPR induction. A lack of glycosylation, specifically within the globular head domain of HA, is directly associated with an increased UPR response. Stepwise addition of glycosylation sites to the globular head of HA in A/X-31 (H3N2) reduces airway inflammation and pathology in infected mice, caused by reduced ER stress gene expression [69]. Similar observations have also been made for avian H5N1 IAV infection, where removal of glycans from the HA globular head increases UPR activation [67, 70]. Adding glycosylation sites to the 1918 H1N1 HA globular head similarly attenuates viral replication in mice, while deletion of HA glycosylation sites N142 and N177 from A/Solomon Islands/2006 increases virulence [71]. Although in this instance the role of the UPR remains unconfirmed, similar phenotypic responses to infection with the H3N2 and H5N1 glycosylation

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mutants suggest modulation of the UPR is a plausible mechanism. The role of individual glycosylation sites in determining productive protein folding of HA has long been established [72]. An absence of glycosylation sites in the globular head domain can reduce calnexin or calreticulin binding at parts of the protein whose folding relies on chaperones, such as near disulfide bonds, and subsequently increase aggregation of misfolded proteins [72]. Absence of glycosylation in the globular head is typical of pandemic influenza strains that arise from zoonotic spillover; the less severe, seasonal strains often acquire mutations in HA that increase the number of glycosylation sites [73-76]. Although certainly not the only factor, increased activation of the UPR is partially responsible for the increased pathogenesis observed in pandemic strains of IAV [69]. Critically however, extensive glycosylation of HA has long been associated with IAV virulence due to its additional effects on receptor binding, fusion, cleavage, and immune evasion [70, 77, 78], as well as increased collectin binding and hence virus neutralisation [79]. The exact extent to which differential activation of the UPR due to changes in HA glycosylation impacts pathogenesis remains unclear.

Glycosylation is also critical for NA, although this has not been studied as extensively as for HA. Glycosylation site deletions increase the ability of NA from A/Puerto Rico/8/1934 (H1N1) to induce ER stress [53]. Deletion of the N219 glycosylation site from NA of another H1N1 virus, A/WSN/1933, similarly increases UPR markers and retention of NA within the ER [68]. Whether UPR activation is a desirable or undesirable outcome that may contribute to a tendency for IAV viral glycoproteins to acquire glycosylation mutations remains to be determined.

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RSV

RSV has two surface glycoproteins: the attachment glycoprotein (G) and the fusion glycoprotein (F). The F glycoprotein of RSV interacts and binds strongly with BiP [80], and is therefore the major contributor to UPR activation in RSV infection [81, 82]. In contrast to IAV glycoproteins, mutations that remove glycosylation sites from RSV F seem to have little effect on UPR activation. Although mutations that remove glycosylation sites typically affect the stability and transport of glycoproteins, the F protein of RSV is an exception. Glycosylation site deletion variants of the F protein are still efficiently transported to the cell surface [81, 82]. However, RSV infection in Hep2 and Vero cell lines show different expression of ER stress genes from the PERK arm of the UPR [69]. The RSV F protein is improperly glycosylated in Vero cells, suggesting differential glycosylation of RSV F is the driving factor distinguishing the two PERK responses [69]. The mechanistic roles of glycosylation for UPR activation in RSV infection thus requires further attention.

CoV

The CoV spike (S) glycoprotein serves as another example of a viral surface glycoprotein associated with UPR activation. It is the largest structural protein of CoV and is heavily glycosylated. Like many viral surface glycoproteins, the S protein mediates cellular attachment and possesses fusion activity that permits cell entry. The cellular target for the S protein varies across different CoV strains. During CoV infection the S protein activates the UPR, although the underlying mechanisms are strain specific [83]. Expression of SARS-CoV-1 S is linked to activation of the PERK pathway, increasing expression of ER stress chaperones [83, 84]. The PERK pathway is similarly induced by HCoV-HKU1 S. However, although PERK activation can

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be attributed to a central region spanning amino acids 201-400 on the S1 subunit of the SARS-CoV-1 S protein, this is not the case for HCoV-HKU1 S [85]. This speaks to independently evolved tendencies to activate PERK across the various CoV strains. That activation of the UPR from the S protein of SARS-CoV-1 and SARS-CoV-2 can be attributed specifically to regions of the S1 subunit suggests that in the case of the S protein, glycosylation is not critical for UPR activation [85, 86].

Summary

Glycosylation of viral proteins has complex links with UPR activation, being important only for a subset of viral glycoproteins and glycosylation sites. This is unsurprising, given the complex and diverse roles played by site-specific glycosylation in protein folding and function. Our limited understanding of the complex interactions between viral protein glycosylation and the UPR highlight the need for further research. In particular, although research into the surface glycoproteins of the IAV HA and CoV S glycoproteins is extensive, knowledge of the surface glycoproteins of other respiratory viruses remains comparatively inadequate. For instance the E3-19K glycoprotein of AdV is known to specifically trigger IRE1 while having no effect on the two remaining signalling cascades [87], although the mechanisms behind this specific activation are unclear. As these viral glycoproteins often activate specifc arms of the UPR, they represent one mechanism viruses can use to subvert the UPR to their advantage. Collectively, the surface glycoproteins of respiratory viruses are the major – but not only – means by which these viruses modulate the UPR.

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Alternative Mechanisms of UPR modulation by viruses

Beyond their surface glycoproteins, respiratory viruses have many structural or accessory – often ER-resident – proteins that have the capacity to specifically induce or inhibit individual arms of the UPR. These proteins often serve immunomodulatory roles, mediating viral-host interactions. In particular, these proteins help viruses balance activation of the branches of the UPR to maximise advantageous outcomes while minimising detrimental processes.

Viroporins

Notable amongst accessory viral proteins are a class of viral ion channels known as viroporins [88]. Viroporins are viral transmembrane pore proteins that regulate membrane permeability, contributing to many aspects of the viral replication cycle. They are thought to influence activation of the UPR by disrupting ER Ca^{2+} homeostasis and hence protein folding [89, 90].

The viroporin M2 is present in all influenza viruses. In IAV, M2 mainly serves as a proton channel [91]. Acting as a regulator of pH across the viral membrane, and also across the trans-Golgi membrane of infected cells, M2 is critical to IAV replication [91]. Interestingly, co-expression of M2 and HA increases the retention of HA within the ER, although curiously with no evidence of UPR activation. Blocking M2 activity with the ion channel blocker amantadine reverses this effect [92]. Thus, equilibration of pH between the cytoplasm and the Golgi by the M2 ion channel protein inhibits intracellular transport of viral membrane glycoproteins such as HA from the ER to the Golgi. Expression of another putative influenza viroporin, PB1-F2, from highly pathogenic avian H5N1 IAV in chickens attenuates virulence and downregulates entire gene clusters associated with the ER stress pathway, with the exception of ERN1, which encodes IRE1α [93, 94]. The extent to

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which this is applicable to typical human IAV infections is unknown, although in mammalian systems PB1-F2 contributes to, rather than attenuates, pathogenesis and virulence [95, 96]. This may in part be attributable to varied expression of PB1-F2 across different viral isolates [97].

Another viroporin, the small hydrophobic non-structural (NS) 2B protein of RV-16, is associated with non-canonical UPR activation [98]. The NS2B proteins of many enteroviruses are Ca^{2+} selective and help trigger viral release by increasing free Ca^{2+} concentrations [98, 99]. RV-16 infection and NS2B expression both induce phosphorylation of PERK and proteolysis of ATF6 [98]. Rather interestingly, although Ca^{2+} release from the ER initiates both PERK and ATF6, IRE1 is not induced, and is in fact inhibited, both during infection and 2B expression [98].

Other examples of non-canonical UPR activation by viroporins are evident in CoVs. The Orf3a protein is present in both sarbecoviruses, although sharing only 73% sequence homology [100]. The SARS-CoV-1 Orf3a viroporin, a K^{+} selective channel important in viral release, only activates PERK [101, 102]. In contrast, the SARS-CoV-2 Orf3a protein, which is instead a non-selective Ca^{2+} channel, induces the ATF6 and IRE1 signalling cascades and is associated with apoptosis [100, 103, 104]. It is unclear whether another viroporin from SARS-CoV-1, the Orf8a protein, elicits any specific UPR arm. In the early-stages of the SARS-CoV-1 outbreak its genome was found to contain a single Orf8ab protein, but due to a nucleotide deletion this protein became two in the later stages of the outbreak: Orf8a and Orf8b [105]. The Orf8ab protein binds to the lumenal domain of ATF6 and induces increased expression of ATF6 associated ER-chaperones BiP, GRP94 and calreticulin [105]. Additionally, Orf8b, which does not possess ion channel activity, forms

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insoluble protein aggregates which trigger the UPR [106]. The Orf8a protein, however, has not yet been associated with the UPR.

The envelope (E) protein of many CoVs has rather interesting effects on the UPR during infection. In many CoVs the E protein is a cation-selective ion channel and assists in viral budding, trafficking, and morphogenesis [107]. In SARS-CoV-1, the E protein localises to the ER-Golgi intermediate compartment where it is associated with Ca^{2+} release [108]. Critically, in infection with SARS-CoV-1 lacking the E protein, 25 stress response genes associated with the IRE1 pathway are upregulated, which can be reduced with complemented expression of the E protein [109]. Further still, the SARS-CoV-1 E protein can alleviate activation of the UPR by chemical inducers thapsparagin and tunicamycin, and in RSV infection [109]. The mechanisms linking Ca^{2+} release to UPR suppression remain to be determined. The E protein is not the only viroporin associated with UPR inhibition. The small hydrophobic (SH) protein of RSV is another viroporin that can inhibit UPR and ER-stress associated apoptosis [110-112]. The effect of the SH protein of the closely related HMPV on the UPR has not been reported.

Accessory Proteins

Many other viral proteins without ion channel activity have been associated with regulation of the UPR. Indeed, several CoV ER-Golgi resident accessory proteins have been implicated in selective induction of ER stress pathways [113]. SARS-CoV-1 Orf6 and Orf7a upregulate ER chaperone GRP94 and induce ER stress-mediated apoptosis [114]. In SARS-CoV-2 infection the Orf8 accessory protein can activate the ATF6 and IRE1 branches of the UPR, but not PERK [115]. SARS-CoV-2 non-structural proteins (nsp) nsp4 and nsp3.1 (an *N*-terminal truncation of nsp3) are

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both involved in tuning the UPR [116]. ATF6 activation is induced by nsp4, and nsp3.1 is involved in the suppression of PERK, specifically at later stages of infection [117].

Accessory proteins can also inhibit the UPR. PERK phosphorylation is inhibited in IAV infection, though the mechanism is not clear [118]. However, the IAV NS1, an RNA-binding protein and inhibitor of host IFN response, can inhibit the PERK pathway; through dsRNA binding it inhibits PKR, another activator of eIF2α phosphorylation [119]. NS1 further relieves ER stress to levels beneficial to IAV replication by binding pre-mRNA processing protein CPSF30 and suppressing XBP1 [53]. The ability of NS1 to inhibit UPR activation is thought to be specific to certain strains such as A/Puerto Rico/8/1934, in which the NS1 protein binds more strongly to CPSF30 [53].

Indirect Mechanisms

Viruses exhibit many mechanisms beyond direct protein interactions that can impact the UPR. CoVs, as positive-sense single stranded RNA viruses, exploit replication organelles (ROs) derived from the ER membrane for viral replication. Negative-sense single stranded RNA viruses such as PIV and RSV also use the ER for replication, remodelling the organelle to form inclusion bodies [120]. These processes are associated with damage to the ER, and subsequently induction of ER stress [121, 122]. The UPR also crosstalks with innate immunity signalling pathways [123, 124]. Toll-like receptors (TLRs) that are associated with recognising pathogen/damage associated molecular patterns in infection and the production of pro-inflammatory cytokines, have been associated with UPR activation [125, 126]. TLR2 and TLR4 signalling specifically activate the IRE1 pathway [127]. Activation of IRE1 in ER stress, in concert with TLR-signalling, is required for the efficient and persistent production of proinflammatory cytokines in macrophages [127].

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Febrile hyperthermia, a common symptom of many respiratory infectious diseases, may exacerbate UPR activation [128]. Protein folding is extremely sensitive to changes in temperature, and while the heat shock response is the principal cellular response to increased temperature, the UPR is also implicated [129]. Hypoxia is another factor commonly induced in respiratory viral infections, by manipulation of hypoxia-inducible factors to support viral replication [130]. Hypoxic conditions, and the associated deficiency in cellular energy, protein synthesis, and disulfide-bond formation, all act to disturb ER homeostasis and stimulate the UPR [131, 132]. Translational shutoff is a common strategy used by many viruses to reduce the synthesis of host proteins [133-136]. This is generally achieved either by directly co-opting host translation machinery or inducing degradation of host mRNA [137]. In doing so, the protein translational load within the ER is greatly reduced, alleviating the pressures that induce the UPR. Some viruses may use these strategies to prevent or limit activation of the UPR to permissible levels.

Role of the UPR in Viral Replication and Pathogenesis

Respiratory viruses modulate ER stress through several distinct mechanisms. In some cases, separate virus strains have independently evolved mechanisms to specifically induce the same signalling cascades. It is therefore worth considering whether these viruses benefit or are disadvantaged by these responses, and further, what effect this may have on disease pathogenesis. Respiratory viruses tightly regulate UPR-associated pathways, striking a balance between upregulation of positive factors such as host protein translational shutoff and ER proteostasis, and the more negative factors associated with inopportune cell death, immune activation and ER protein degradation [53].

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Overloading of ER glycosylation pathways and subsequent accumulation of under-glycosylated proteins that tend to misfold is one of the critical mechanisms that causes UPR activation in respiratory virus infection. Perturbations of cellular glycosylation pathways are therefore to be expected before the host cell restores ER homeostasis. Hence, the UPR acts as a pathway through which these viruses are able to promote glycosylation of viral and host glycoproteins. XBP1s is specifically linked to induction of *N*-glycan maturation machinery in an attempt to increase protein clearance from the ER, as well as cell type-dependent changes to glycan microheterogeneity [138, 139]. ER chaperones play an important role in the processing of ER-resident proteins, including viral membrane proteins, and are upregulated in response to the UPR to re-establish ER homeostasis. ER chaperones are also beneficial to viruses as they create a permissible environment more tolerant to mutations, as often occurs in viral proteins eventuating in immune escape, that would otherwise reduce the overall protein fitness [140].

Under irremediable ER stress, the host cell is primed towards the pathway of apoptosis, triggered by the NF-κB / JNK signalling downstream of IRE1, or by the CHOP pathway downstream of PERK [141]. Apoptosis early in viral infection can limit viral replication, whereas at later timepoints, or in specific cell types, apoptosis can be weaponised for cell death to spread viral particles. The UPR, while not the only signalling cascade driving apoptosis, offers a suitable pathway for respiratory viruses to exploit apoptosis. Prolonged UPR activation is also associated with many facets of disease pathogenesis in respiratory disease [142-144]. Airway fibrosis, inflammation and hyperresponsiveness are linked to the induction of ER stress in allergic asthma [145]. Additionally, XBP1 pathways promote epithelial to mesenchymal cell transitions typical of

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pulmonary fibrosis [146], and IRE1β is functionally required for mucin production and could potentially play a role in mucin overproduction in many respiratory diseases [147, 148]. IAV, RSV, and CoV infections display varied UPR, and there is strong evidence to suggest the specific responses they achieve are associated with advantageous outcomes for the virus (Figure 2).

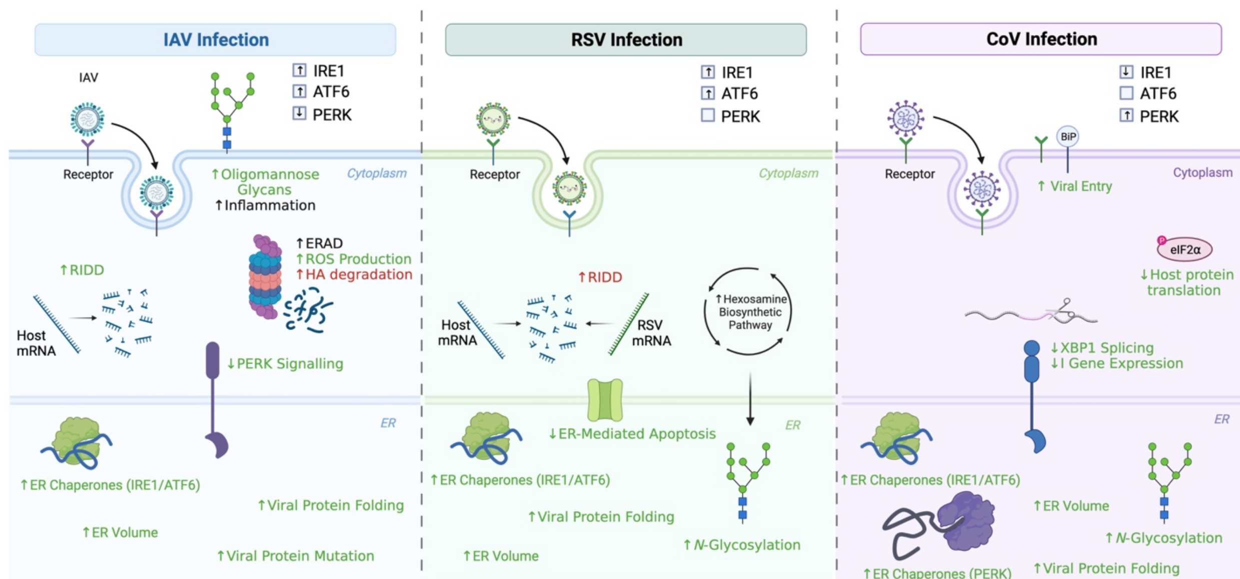

Figure 2. Non-canonical UPR in common respiratory viral infections with IAV, RSV and CoV. At the top of the panel, the individual arms of the unfolded protein response (UPR) typically involved with each infection is shown, with arrows indicating the direction of activation that is most commonly attributed to infection with each virus. Terms in green represent responses typically beneficial towards viral replication, and terms in red indicate responses detrimental towards viral replication. The CoV response broadly represents changes observed across all human coronaviruses. Abbreviations: ATF6: activated transcription factor 6, BiP: binding immunoglobulin protein, CoV: coronavirus, eIF2α: eukaryotic initiation factor 2α, ERAD: ER-associated degradation, HA: haemagluttinin, IAV: influenza a virus, IRE1: inositol-requiring enzyme 1, PERK: PKR-like ER kinase, RIDD: regulated IRE1-dependent decay, ROS: reactive oxygen species, RSV: respiratory syncytial virus, XBP1: x-box binding protein. Created with BioRender.com.

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IAV

The IRE1 arm is the principal UPR arm activated in IAV infection. Activation of this signalling cascade is important for efficient replication of IAV, although the exact mechanism is unclear [66, 149]. Of the myriad responses downstream of IRE1 activation, not all elements are necessarily beneficial to IAV. For instance, upregulation of ERAD-associated mannosidases in IAV infection results in increased HA degradation and hence decreased IAV replication [50, 65]. However, IRE1 can also trigger ER expansion and increased expression of ER chaperones that are beneficial to the virus due to the subsequent increase in the folding efficiency of ER-resident IAV proteins. For instance, folding of HA requires the calnexin chaperone system, including chaperones such as ERp57 which are upregulated in ER stress [51, 150, 151]. Additionally, upregulation of chaperones increases the mutational tolerance of HA. As HA is the most abundant surface IAV protein, increased tolerance to HA mutations increases its capacity to escape immune recognition [140].

ERAD itself may benefit IAV replication by increasing the production of reactive oxygen species and creating a redox state beneficial for ER oxidoreductase activity, viral glycoprotein disulphide bond formation and folding, and hence viral replication [152, 153]. Increased ERAD also increases degradation of MHC class I (MHC-1) proteins involved in immune recognition [154]. An activated UPR impairs cell surface expression of MHC-1 and may contribute to the downregulation of MHC-1 observed in infection with IAV [155, 156].

IAV additionally uses cross-talk between the separate arms of the UPR to its benefit. The IRE1 induced P58^{IPK}, an inhibitor of eIF2α kinases such as PERK and PKR, prevents the phosphorylation of eIF2α and thereby sustains the translation of viral mRNA in IAV infection

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[157], and also serves to repress the pro-apoptotic PERK axis [158]. With PERK typically suppressed in IAV infection, UPR-associated apoptosis is largely driven by the IRE1-associated JNK and caspase-12 pathways [151]. ER-stress mediated apoptotic responses may also differ depending on the host cellular environment. Cells expressing the IFN-inducible human myxovirus resistance gene A (MxA) experience enhanced cell death via the UPR in IAV infection [159].

UPR induces pathogenesis in IAV infection by driving fibrogenesis in lung epithelial cells and is associated with acute lung injury in mice [69, 151]. Rather interestingly, another mechanism by which the UPR impacts disease severity in IAV infection is through XBP1s activation inducing a shift towards oligomannose host *N*-glycans, with a corresponding increase in mannan-binding lectin-mediated inflammation [160].

RSV

Although the IRE1 signalling cascade is typically activated in RSV infection, in stark contrast to IAV, this signalling cascade inhibits RSV replication. RSV infection activates the hexosamine biosynthetic pathway and upregulates *N*-glycosylation in the ER via the XBP1s pathway [161]. The upregulation of glycosylation machinery increases the processing of RSV glycoproteins, an overall beneficial response for the virus. Responses downstream of XBP1 splicing are not able to explain the inhibitory effect associated with IRE1 activation, and instead RIDD is the likely mechanism behind this inhibition [59]. While the regulated decay of host ER-targeted mRNA could be considered beneficial to the virus, RSV mRNA is unable to escape being degraded, which ultimately serves to inhibit viral replication.

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In RSV infection, stark differences are evident in regard to the effect of UPR modulation on replication *in vitro* and *in vivo*. For instance, deletion of the UPR-suppressing RSV SH protein is dispensable in tissue but accompanies a 10-fold decrease in replication efficiency in the upper respiratory tract of mice [162]. RSV infection induces ER stress-mediated apoptosis through the caspase-12 and caspase-3 pathway [116]. However, RSV also utilises its SH protein to partially suppress ER-mediated apoptosis, a protective effect that may help the virus avoid host immune detection [112].

Although IRE1 and ATF6 activation are typical of RSV infection, in PERK-deficient mice RSV infection results in lower counts of myeloid and activated CD4 and CD8 T cells, mucous production, and cytokine responses [63]. This suggests PERK activation is associated with increased immune recognition in RSV infection. In addition to the role of the UPR in RSV replication and immune replication, ER stress responses also induce mesenchymal transition in human small airway epithelial cells, a hallmark of pulmonary fibrosis, highlighting the importance of the UPR for disease pathogenesis in RSV infection [161].

CoV

In contrast to RSV and IAV infection, the human CoVs demonstrate a distinct UPR profile. Three human coronaviruses (MERS-CoV, HCoV-OC43 and SARS-CoV-2) replicate efficiently in IRE1 deficient cells, suggesting IRE1 activation is not necessary for CoV replication [163]. Extensive and prolonged induction of IRE1 in CoV infection may in fact favour a pro-apoptotic response rather than beneficial responses such as increased chaperone expression aimed at restoring homeostasis [163]. Although SARS-CoV-2 induces IRE1, downstream XBP1 splicing is actually

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suppressed by the virus, perhaps to limit cytokine signalling that could trigger detection by the host immune system [163]. SARS-CoV-1 selectively activates PERK rather than IRE1, to promote its replication. PERK-associated ER chaperones are upregulated via eIF2α, while CHOP, the apoptosis-associated and hence less beneficial arm of the UPR, is induced to a much lesser degree [84, 101]. In SARS-CoV-2 infection, although increased levels of CHOP are observed, it is evident only in more susceptible cell lines and at later timepoints of infection [164]. Activation of PERK in CoV infection also attenuates host protein translation, including - in the instance of SARS-CoV-1 infection - cytokines such as CXCL2 and type I interferon signalling [83, 101, 115, 165, 166]. As prolonged PERK activation may lead to apoptosis, PERK may be suppressed by the virus later in infection, as with the SARS-CoV-2 nsp3.1 [117].

Although proapoptotic effects of PERK may be balanced by CoVs, UPR-associated apoptosis in CoV infection is still largely associated with this arm of the UPR. MERS-CoV infection of mice microvascular endothelial cells, but not fibroblasts, induces apoptosis through UPR associated pathways, demonstrating MERS-CoV modulation of apoptosis is restricted to some cellular environments [167]. Manipulation of the UPR within these cells reduces viral replication, and further improves the respiratory function of these mice [167]. Inhibition of PERK signalling in MERS-CoV infection, and thus proapoptotic signalling, ameliorates disease severity and pathogenesis [168]. Similar to what is observed in IAV and RSV, UPR-associated apoptosis in CoV infection induces inflammation and epithelial damage [86, 169]. UPR-associated apoptosis is also associated with increased neurovirulence in HCoV-OC43 infection of human neuronal cells, indicating UPR-associated pathogenesis extends beyond the respiratory system [170].

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Although PERK is the UPR arm most commonly associated with CoV infection, there is also evidence for the involvement of IRE1 and ATF6. Simultaneous inhibition of IRE1 and ATF6 prior to SARS-CoV-2 infection reduces virion release [171]. In SARS-CoV-2 infection, proteomic analyses revealed that increased expression of glycosylation machinery and *N*-glycosylation, typically associated with XBP1s, coincides with activation of the UPR [164]. Although as a chaperone BiP is typically localised within the ER, when upregulated as a result of the UPR, BiP can escape ER retention and become localised at the cell surface where it is able to serve as a receptor for viral cell entry [172-174]. BiP, as a critical ER chaperone and component of the UPR, is commonly upregulated under ATF6 and other UPR pathways, and has been identified as a strong marker of CoV infected patients, including patients with COVID-19 [55, 175, 176]. In MERS-CoV infection, cell surface BiP acts as an attachment factor for the virus, positively regulating viral entry in permissive cells [177]. Similarly, BiP regulates ACE2 cell surface expression and directly binds SARS-CoV-2 S and ACE2 to form a complex that promotes viral entry [178]. CoVs likely benefit from IRE1 and ATF6, with compensatory crosstalk between these arms explaining the efficient replication observed when they are individually knocked-down.

Host Factors

In many diseases designated as common co-morbidities of viral respiratory diseases it is common to observe chronic activation of the UPR. Chronic inflammation is observed in obesity due to activation of ER stress in response to dysregulated proteostasis, perhaps contributing to the increased disease severity observed in obese individuals during respiratory viral infection [179, 180]. In another frequent co-morbidity, type 2 diabetes, chronic activation of the UPR is also observed [142]. UPR dysregulation is a hallmark of many cancers, respiratory and

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neurodegenerative diseases, and aging, potentially predisposing individuals with these conditions to more severe disease through the UPR axis [27, 181].

Sex is a confounding factor in the pathogenesis of many viral respiratory diseases. Although insights into the intersection of sex hormone signalling and sex-determinant genes on immune responses have certainly progressed, we still lack an understanding of the molecular mechanisms underlying disparities in disease outcomes. Despite limited research into sex-differentiated responses of the UPR in respiratory viral infection, recent reports demonstrate the value of considering sex in understanding disease pathogenesis. A recent study investigating the differential transcriptomic responses to IAV infection in male and female ferrets, the closest analogue to human pathogenesis, identified a key role of the UPR in sex biases [182]. Female ferrets demonstrate a more rapid and robust immune response coinciding with rapid induction of XBP1s [182]. In mammals, females typically have higher IAV-associated mortality [183]. Both male and female ferrets were neutered in this study to eliminate additive effects of sex hormones, highlighting the key importance of the UPR axis in sex-biased influenza pathogenesis. Nonetheless, sex hormones are directly associated with the UPR. Estrogen signalling directly triggers the UPR by causing Ca^{2+} ion efflux from the ER into the cytosol, and indirectly by regulating expression of UPR components such as BiP and XBP1 [184]. Activation of the UPR by estrogen is hypothesised to limit COVID-19 pathogenesis in females by reducing the burden of ER stress, but this remains to be validated [185].

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Treatment

Respiratory viruses have evolved to balance selective activation of the UPR, benefiting from responses that promote replication and limiting inhibitory responses. Hence, the therapeutic potential of pharmacological agents that modulate ER stress in reducing the severity of respiratory viral diseases is clear. This therapeutic strategy has been of increasing interest, particularly during the ongoing COVID-19 pandemic [186, 187]. Treatment with the asthma medication Montelukast stimulates the PERK signalling cascade, which is typically suppressed in IAV infection, and suppresses IAV gene expression [118]. Thapsigargin inhibits the replication of CoVs and IAV by reactivating ERAD and other quality control pathways that are typically downregulated in infection [188, 189]. Even cannabidiol has been implicated in the inhibition of SARS-CoV-2 infection, mechanistically through the induction of the IRE1 arm of the UPR [190]. Further research is required to investigate the potential therapeutic impact of many pharmacological compounds that disrupt specific aspects of the UPR, as it also clearly serves a critical role in the replication and pathogenesis of these viral respiratory diseases. Any potential therapeutic intervention targeting the UPR would need to ensure that the balance of the impact on the host and virus is in the host's favour.

Conclusion

Respiratory viruses have many strategies to modulate the UPR to elicit non-canonical responses. These viruses depend on balancing the host ER stress responses to maximise beneficial processes in proteostasis, whilst minimising detrimental quality control and immune recognition systems. This balance is largely achieved through the direct specific effects of viral surface glycoproteins but can also be modulated by the indirect effects of other viral proteins. Furthermore, prolonged

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activation of the UPR in the respiratory system is generally detrimental for disease pathogenesis, further exemplified by the prevalence of chronic UPR activation in common co-morbidities and predisposing factors for respiratory viral diseases. The therapeutic potential of harnessing the UPR axis in treating respiratory viral diseases highlights the need to further our understanding of the complex interactions underlying ER stress in viral infection.

Author Contributions

All authors wrote and reviewed the manuscript. KLM designed the figures.

Declaration of Interest

The authors report there are no competing interests to declare.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Data Deposition

This article does not create or analyse new data, therefore no data sets were deposited

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