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Full length article

Endoplasmic reticulum as a potential therapeutic target for covid-19 infection management?

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ABSTRACT

In December 2019, many pneumonia cases with unidentified sources appeared in Wuhan, Hubei, China, with clinical symptoms like viral pneumonia. Deep sequencing analysis of samples from lower respiratory tract revealed a novel coronavirus, called 2019 novel coronavirus (2019-nCoV). Currently there is a rapid global spread. World Health Organization declare the disease a pandemic condition. The pathologic source of this disease was a new RNA virus from Coronaviridae family, which was named COVID-19. SARS-CoV-2 entry starts with the binding of the spike glycoprotein expressed on the viral envelope to ACE2 on the alveolar surface followed by clathrin-dependent endocytosis of the SARS-CoV-2 and ACE2 complex. SARS-CoV-2 enters the cells through endocytosis process, which is possibly facilitated, via a pH dependent endosomal cysteine protease cathepsins. Once inside the cells, SARS-CoV-2 exploits the endogenous transcriptional machinery of alveolar cells to replicate and spread through the entire lung. Endosomal acidic pH for SARS-CoV-2 processing and internalization is critical. After entering the cells, it possibly activates or hijack many intracellular pathways in favor of its replication. In the current opinion article, we will explain the possible involvement of unfolded protein response as a cellular stress response to the SARS-CoV-2 infection.

Opinion

Currently, there is no specific and effective antiviral therapy for covid-19 and patients are offered only supportive therapy (Chen et al., 2020). To curb the spread of the disease, measures aimed at controlling the potential sources of infection and early diagnosis are followed, while proper personal hygiene, supportive treatment and the clear publication of epidemic information are also recommended. From a public health perspective, there is an urgent need to find antiviral therapies and to develop an effective vaccine to stop or at least limit the pandemic caused by Covid-19. In this sense, working on the development of antivirals that target essential elements of viral replication

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cycle requires an intensive research.

The main function of the endoplasmic reticulum (ER) in eukaryotic cells is to synthesize and fold the transmembrane proteins (Ghavami et al., 2018; Iranpour et al., 2016; Yeganeh et al., 2013) and those that are going to be secreted and regulate secretome of the cells (Logue et al., 2018; Talty et al., 2019). However, entry of excess amount of proteins to the ER protein folding system disrupts the balance between protein synthesis demand and ER folding capacity, resulting in the accumulation of the unfolded proteins in the lumen of the organelle. Continued accumulation of the unfolded proteins in the ER lumen triggers ER stress response, which is initiated to help the organelle return to homeostasis (Almanza et al., 2019). The changes in the ER initiate the activation of signalling pathways known collectively as the unfolded protein response (UPR) (Almanza et al., 2019; Hombach-Klonisch et al., 2018; Yeganeh et al., 2015).

The UPR response is mediated by three ER transmembrane sensors: the protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), the activating transcriptional factor 6 (ATF6), and inositol-requiring enzyme 1 alpha (IRE1α) (Lee et al., 2003; Mehrbod et al., 2019; Shi et al., 1998; Szegezdi et al., 2006; Wang et al., 2000). Specifically, these sensors are transmembrane proteins with an intraluminal domain that recognizes unfolded proteins inside the ER, and a cytosolic domain that will transmit the signal and activate the subsequent response. UPR resolves ER stress by diverse mechanisms, to improve ER folding capacity by inducing the expression of molecular chaperones, a reduction in the global protein synthesis to reduce their influx into the ER and ER-associated degradation (ERAD) (REF). However, if the ER stress persists and is not resolved, UPR may lead to activation of signalling pathways that induce apoptosis (Ghavami et al., 2014; Szegezdi et al., 2006; Tabas and Ron, 2011).

The replication of coronaviruses takes place in the cytoplasm and is directly related to the ER. Diverse studies have shown that the replication of coronavirus induces ER stress and, consequently, UPR in infected cells. UPR modulates a wide range of signalling pathways that are essential to the cell function such as the mitogen-activated protein (MAP) kinase pathways, inflammatory responses, apoptosis, autophagy and innate immunity. Thus, it is not surprising that the existence of ER stress/UPR can significantly affect the patient's antiviral response and is a key factor in virus-host interaction (Fung and Liu, 2019; Ma et al., 2018; Shi et al., 2019; Zou et al., 2019).

ER stress has been evident in cells infected with various viruses, including: severe acute respiratory syndrome coronavirus (SARS-CoV), Murine hepatitis virus (MHV), avian infectious bronchitis virus (IBV) (Chan et al., 2006; Fung and Liu, 2019; Liao et al., 2013; Shi et al., 2019; Versteeg et al., 2007; Yeung et al., 2008). The likely mechanisms responsible for ER stress and induction of UPR response upon coronavirus infection is excessive synthesis, modification and folding of viral proteins; the severe restructuring of the ER membrane for the formation of double membrane vesicles (DMVs) for viral genome replication; and the exhaustion of the ER membrane due to continued formation of new virions and autophagy (Fung et al., 2014; Fung and Liu, 2014). Different coronaviruses have developed the ability to subvert or utilize certain aspects of UPR and overcome protein translation shutdown to benefit their own replication and pathogenesis by ensuring the production of viral proteins (Fung et al., 2016).

In one study, it was analysed in SARS-CoV how the early secretory pathway interacts with the induction of a reticulovesicular cytoplasmic network and the viral replication/transcription complex that is anchored to this network (Knoops et al., 2010). Treatment with brefeldin A, a drug that prevents the assembly of proteins of the Coatomer Protein I (COP–I) complex, hence disrupting the transport from the ER to the Golgi complex, partly inhibited reticulovesicular network formation and viral RNA synthesis, but did not completely block viral RNA synthesis. The authors conclude that a reduced level of reticulovesicular cytoplasmic network formation can be maintained in the presence of brefeldin A, suggesting that the early secretory pathway is unlikely to be intimately involved in coronavirus replication.

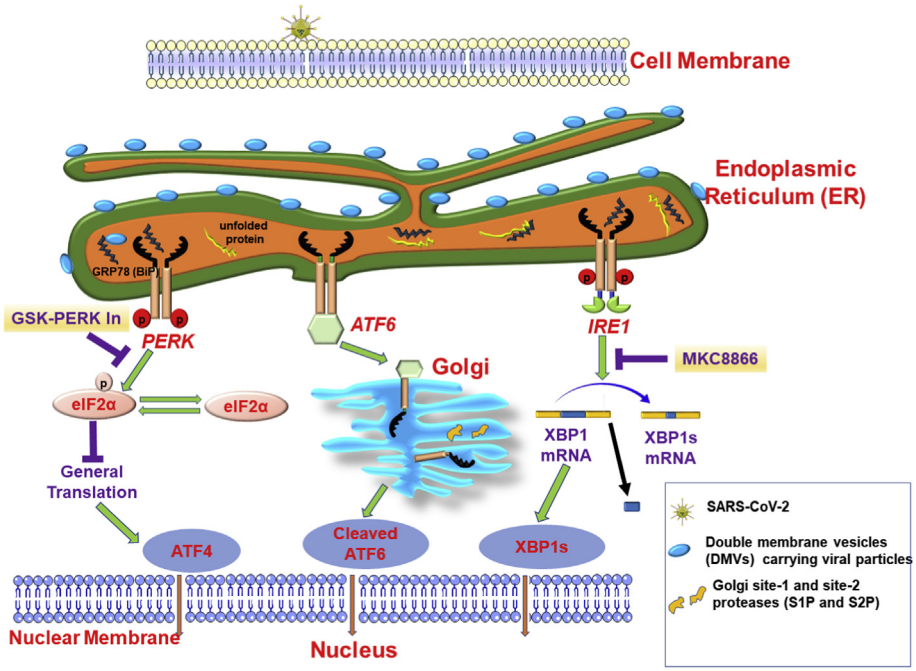
Another work reported that delayed brain tumour cell line infected by MHV responded with the activation of both IRE1 and ATF6 pathways evidenced by an IRE1-mediated splicing of XBP-1 (X-box binding protein 1) mRNA and the cleavage of ATF6 (Bechill et al., 2008). However, a reduced induction of downstream UPR target genes was observed. Ultimately, the virus alters the UPR, preventing the induction of UPR-responsive genes, which induces the blockage of protein synthesis in the host cell and favours the translation of viral proteins. This modified response would allow MHV to escape the innate defence cell signalling pathways during coronavirus replication. In yet another project, researchers investigated the capability of porcine epidemic diarrhoea virus (PEDV) infection to induce UPR in Vero cells (Wang et al., 2014). They have shown that, the presence of the virus in the cell induced a UPR, while the silencing of PERK by shRNA considerably increased virus loads in the cells. The treatment with an ER stress inducer, 2-deoxy-D-glucose (2-DG), reduced the degree of PEDV infection via altering viral protein translation during the early stage of virus infection and reducing the virus assembly. The antiviral effects of an small compound inhibitor, named K22 ((Z)-N-(3-(4-(4-bromophenyl)-4-hydroxypiperidin-1-yl)-3-oxo-1-phenylprop-1-en-2 yl)benzamide), that specifically targets this membrane-bound RNA replication step by blocking the formation of DMVs was assayed in primary human epithelia cultures (Lundin et al., 2014). K22 exerted strong anti-coronavirus activities, including SARS-CoV and MERS–CoV, during the early stages of infection through severe loss of DMV formation resulting in almost complete inhibition of RNA synthesis.

It has been reported that in severe cases of COVID-19, hypoxaemia is induced by the pneumonic process and might have several adverse effects in patients (Rello et al., 2020). There are several lines of defence mechanisms in response to hypoxia, which is a consequence of hypoxaemia, including responses triggers from mitochondria and ER (Bartoszewska and Collawn, 2020). The main goal of these responses to hypoxia is restoring oxygen level and promoting cell survival in these conditions (Bartoszewska and Collawn, 2020). Therefore, in prolonged hypoxia induction via COVID-19, the UPR is triggered to help the cells to survive. However, prolonged hypoxia would possibly drive UPR role from survival to death and apoptotic mode, which possibly is one of the causes of cellular and organ damage in COVID-19 cases.

Recent investigation has showed that IRE1 axis of UPR is involved in regulation of the secretome of the cells via production of spliced XBP (XBPs) (Logue et al., 2018). The investigators have developed a specific inhibitor, which competitively inhibits RNAase activity of IRE1 (Logue et al., 2018; Sanches et al., 2014) and showed that it inhibits secretome of the breast cancer cells (Logue et al., 2018). On the other hand, recent reports indicate that SARS-Coronavirus induces UPR through its Open Reading Frame-8b (ORF-8b). It also activates NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasomes in macrophages which is involved in regulation of IL-1β and IL-18. ORF-8b also activates autophagy flux in the infected cells, which might be indirectly involved in regulation of cytokine processing in the infected cells (Shi et al., 2019). Therefore, targeting the RNAase activity of IRE1, could potentially be an ideal approach to modulate Covid-19 infection and pathogenesis via modulation of the secretome of macrophages.

Yet another study has showed that SARS-CoV activated PERK arm of UPR with subsequent increased phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α). Activation of the PERK regulates innate immunity by suppression of type 1 interferon (IFN) signaling (Minakshi et al., 2009). Therefore, it suggests a potential role for UPR in attenuating IFN responses and innate immunity in Coronavirus infected cells. Hence, recently developed potent PERK inhibitors (GSK-PERK inhibitor) could also serve as potential therapeutics for controlling Covid 19 infection.

Several compounds can act as metal ionophores which diffuse through lipid membranes as they transport metal ions between extracellular and intracellular spaces and between different cellular



Scheme 1. SARS-CoV-2 spike protein interacts with the lung epithelial cells through Angiotensin-Converting Enzyme 2 (ACE2) and being internalized to the cells via endocytosis. SARS-CoV-2 uses intracellular trafficking and double membrane vesicles (DMVs) for replication. During the process of viral replication possibly DMVs carrying viral particles interacts with ER chaperons (ATF6 = activating transcription factor 6; IRE1 = inositol requiring enzyme-1; PERK = PKR-like endoplasmic reticulum kinase; GRP78(BiP) = binding immunoglobulin protein). and initiates unfolded protein response (UPR). In addition, the protein load to the ER protein synthesis machinery during viral protein synthesis can possibly induce production of unfolded protein and initiate UPR during SARS-CoV2 infection. Inhibitors of the PERK (GSK-PERK inhibitor) and IRE1 RNAase activity (MKC8866) can regulate the UPR response in infected cells through modulating the innate immunity and the cellular secretome, respectively. Therefore, these inhibitors hold promise as potential therapeutics for controlling Covid-19 infection. [eIF2α = eukaryotic translation initiation factor 2 alpha; XBP1s = spliced X-box binding protein 1].

compartments. Ionophore-metal complexes passes across lipid vesicle membranes, becoming protonated upon entry which triggers the release of the bound metal inside the cellular organelle. This interferes with the acidification of the lysosomal compartment and affects autophagy, leading to the release of degradative enzymes into the cytosol upon disruption of lysosomes, triggering stress and subsequent apoptosis. In Rous sarcoma virus (RSV), metal ionophores (8-Hydroxyquinoline and several of its derivatives) can inhibit proteasome with subsequent disruption of viral replication processes through the inhibition of Ribonucleic Acid-Dependent Deoxyribonucleic Acid Polymerase (Rohde et al., 1976). Zinc (Zn) ionophores can exert their effects on both autophagy (Rohde et al., 1976) and proteasome (Te Velthuis et al., 2010) with their effects being extensively evaluated in cancer (Ding and Lind, 2009) and HIV infection (Lee et al., 2019). The observed effects were due to the inhibition of the RNA-dependent RNA polymerase elongation and template binding. Usage of Zinc and Zinc ionophores may enhance the therapeutic effects of targeting autophagy and replication in COVID-19 by several compounds which along pyrithione include dithiocarbamates, disulfiram and quinoline derivatives such as clioquinol. Since Zn and Zn ionophores interact with both the autophagy machinery and the replicative apparatus in SARS-CoV, such interactions likely involve ER stress and UPR induction.

In summary SARS-CoV-2 can possibly activate UPR and hijack this pathway for the benefit of its own infection process. In Scheme 1 a brief summary of the possible role of autophagy and UPR in SARS-CoV-2 infection is summarized. Considering that the replication of coronaviruses causes ER stress and induces UPR in the infected cells, additional research on coronavirus-induced UPR could help identify new targets for antiviral agents and facilitate the development of effective vaccines against covid-19. Interfering with or manipulating the coronavirus-induced UPR may provide new therapeutic targets that contribute to infection control and the pathogenesis of this emergent coronavirus.

Author agreement

Hereby, all authors agree the publication of the article by European Journal of Pharmacology.

CRediT authorship contribution statement

Antoni Sureda: Writing - original draft. **Javad Alizadeh:** Writing - original draft, participation in revision **Seyed Fazel Nabavi:** Writing - original draft. **Ioana Berindan Neagoe:** Writing - original draft. **Cosmin Andrei Cismaru:** Writing - original draft. **Philippe Jeandet:** Writing - original draft. **Marek J. Los:** Writing - original draft, Writing - original draft. **Emilio Clementi:** Writing - original draft. **Seyed Mohammad Nabavi:** Writing - original draft. **Saeid Ghavami:** Writing - original draft, revision.

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