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Relative Endoplasmic Reticulum Stress in Viral and Bacterial Pulmonary Infection

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Abstract: The endoplasmic reticulum is an essential organelle necessary for synthesis of proteins, folding for export trafficking, and lipid metabolism. It plays a role in depot homeostasis by effectively accomplishing these functions. In most instances, the endoplasmic reticulum properly executes its task of properly folding the proteins it contains. Viral, bacterial, or any other form of cellular injury might also render the endoplasmic reticulum incompetent, thereby deranging protein folding. The unfolded protein response (UPR) restores the ER's normal functioning.

The UPR is a signaling system initiated when there is an aggregation of the misfolded proteins in the ER. Its main branches include the UPR are IRE1, ATF6, and PERK. These processes try to re-establish the normal functioning of the endoplasmic reticulum by enhancing the capability for protein folding, reducing protein production, and bettering protein degradation. If these adaptive processes are not successful and the stress is protracted, the UPR can turn to apoptosis, enabling the cell to self-destruct and prevent further damage. For this reason, the proper function of the endoplasmic reticulum is critical in maintaining intercellular calcium (Ca^{2+}) homeostasis, critical both for cellular signaling and function.

This paper further look into the possibility of how UPR may aid in the treatment of chronic inflammation-related airway issues, since it is involved in airway inflammation and also examines the potential therapeutic benefits of pharmacological interventions targeting these pathways, as well as the role of ER stress in nonmalignant lung illnesses resulting from acute and chronic bacterial and viral infections.

***Keywords**: Endoplasmic Reticulum, UPR, Apoptotic, Inflammation, Airways, Bacterial, Viral, Homeostasis, Therapeutics.*

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I. INTRODUCTION

The endoplasmic reticulum (ER) is a vital organelle for cellular activity in terms of protein and lipid synthesis, folding, modification, and transport. It appears in two forms: rough endoplasmic reticulum that is characterized by the presence of ribosomes, substantially involve in the integration as well as in the alteration of proteins; and the smooth endoplasmic reticulum, devoid of ribosomes, responsible for lipid synthesis, detoxification, and calcium storage. Another major function of the endoplasmic reticulum is to control stress responses, particularly in regard to cellular reaction to protein misfolding through the UPR (unfolded protein response). The ER maintains cellular homeostasis and maximizes cell function by ensuring proper folding and quality of proteins.

The UPR (unfolded protein response) is a physiological stress response that can be cause by pathogens such as bacteria or virus accumulating misfolded proteins in the ER. Pathogenesis and viral replication are significantly impacted by mechanisms, which include the UPR. The ER is usually used by viruses for several stages of their life cycles, such as entrance, assembly, genome replication, in production of proteins as well as in the alteration in the ER. The UPR includes three basic signaling pathways: PERK, IRE1, and ATF6. All these lead to the reestablishment of protein homeostasis. These pathways together orchestrate a complex response to reduce ER stress; however, if the stress is too high or too persistent, the UPR might activate apoptosis to prevent further damage to the cell.

Endoplasmic reticulum stress happens when the ER becomes overloaded with excess unfolded or misfolded proteins, disrupting its normal functions. At physiological conditions, cells respond to low levels of ER stress by adaptive mechanisms including the UPR, which attempt to reverse cell function through enhancement of the folding capacity of proteins and reduction of protein load. However, when stress is maintained or intense, the UPR can become pathological and lead to functional failure in cells. Chronic ER stress is pathologically linked with various diseases. These include neurological ailments including Alzheimer's, Parkinson's, diabetes, cardiovascular conditions and cancer.

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Under such situations, the prolonged ER stress induces inflammation, apoptosis, and impaired cellular metabolism, conditions under which the disease is enhanced. Another related finding is that ER stress facilitates to the advancement of insulin resistance and beta-cell impairment in diabetes and supports the proliferation of tumor by the ability of cancer cells to manage metabolic adversities.

➢ *UPR (Unfolded Protein Response) and its Signaling Pathways*

ER stress can be triggered by the build-up of misfolded proteins in the ER which brings demand for chaperone proteins which include glucose-regulated protein 78 (grp78). The UPR is an important physiological reaction to the amassment of denatured or misfolded proteins in the ER. This response either aims to regain balance within the endoplasmic reticulum or, when persistent, induces apoptosis in the cell to prevent further damage. The UPR is controlled by three main signaling pathways: IRE1, PERK, and ATF6 are three separate sensor proteins embedded in the membrane of the endoplasmic reticulum, each controlling one of these signaling pathways.

- *IRE1 Signaling Pathway:*

RE1 is the most conserved sensor of UPR. Subsequent to the ER stress, IRE1 autophosphorylates and undergoes oligomerization. This splices the cytoplasmic domain of IRE1 into mRNA for XBP1 (X-Box Binding protein-1), which folds to become a strong XBP1s, a strong transcription factor. This second messenger increases the transcriptional activity of genes which participated in folding protein, breakdown, ERAD, and lipid synthesis, with the aim of making the ER better equipped to deal with stress. IRE1 also reads across several mRNAs through the technique known as regulated RIDD (IRE1-dependent decay), thus minimizing the number of proteins traversing the endoplasmic reticulum (ER). Over activation of IRE1 may induce inflammation and apoptosis via interaction with other pathways like JNK and NF-κB [1–3].

- *PERK Pathway:*

PERK **(**protein kinase R-like kinase) phosphorylates the eIF2α (eukaryotic initiation factor 2α) as a result of the stress. This causes attenuation in the synthesis of global proteins temporarily. It lightens the load on the endoplasmic reticulum by slowing down the synthesis of proteins. Meanwhile, selective mRNAs translation continues with ATF4 (activating transcription factor 4). The amino acids articulation, metabolism, antioxidant responses, and autophagy genes is also enhanced by this transcription factor. When stress persists, ATF4 is activated to transactivate apoptosis-inducing proteins such as C/EBP homologous protein (CHOP), culminating in cell death if homeostasis is not restored [4,5].

- *ATF6 or activating transcription factor 6:*

When the ER is stressed, Relocation of ATF6 occurs mainly to the Golgi apparatus where it endures separation by proteases such as site-1 and site-2. The cytoplasmic fragment is a transcription factor which shifts towards the nucleus activating genes that enhance the action of the endoplasmic reticulum, including chaperones and elements of the ERAD pathway. This route is targeted largely for enhancing the folding ability of the endoplasmic reticulum and removing the faulty proteins [6–8].

II. ENDOPLASMIC RETICULUM STRESS IN VIRAL PULMONARY INFECTIONS

Viruses are intracellular particles that replicate their genome using the recipient's cell machinery where proteins are produced from the RNA of the virus, and produce infectious particles. Research has identified specific viral proteins that can use only the extracellular space (ER). Human viruses, for instance, have been shown to utilize membrane of the ER for the purpose of translation, multiplication and also stimulates budding that is skewed toward changing host immunity and cellular membrane transport [9].

For this aim, the present study will focus on Influenza, SARS-CoV-2, Cytomegalovirus, Hepatitis C Virus (HCV), and Respiratory Syncytial Virus (RSV) viruses that are known to have well-characterized interactions with the endoplasmic reticulum and whose influence on human health has been of continuous interest. Each of these viruses is highly researched in relation to their capacities to provoke endoplasmic reticulum stress, influence UPR, and modulate pathways related to cellular processes of reproduction and immune evasion.

➢ *Influenza Virus:*

The Influenza virus causes endoplasmic reticulum stress by overburdening the host cell's endoplasmic reticulum with the fabrication and refinement of viral peptides. The virus hijacks the host's translational apparatus to synthesize its proteins, including as hemagglutinin and neuraminidase glycoproteins, so straining the ability of the endoplasmic reticulum properly to fold and change the proteins, that misfolded proteins start accumulating. This triggers the unfolded protein response (UPR), a biological response aimed at restoring protein-folding balance. The UPR initially attempts to degrade the stress; however, persistent or exaggerated viral protein synthesis may lead to continued ER stress with interruption of cell normalcy [10,11].

The influenza virus has developed mechanisms to exploit the manipulation of the unfolded protein response (UPR), using it to avoid premature apoptosis and enhance viral replication. The activation of ER stress also increases the inflammatory response during the infection, which not only worsens tissue damage but also benefits viral pathogenesis. The relationship between influenza virus and ER stress becomes clear in the easily destabilized balance through which the virus exploits cellular responses to stress for an enhancement of its replication process in ways that could potentially inflict no significant damage upon the host tissue [12,13].

➢ *SARS-CoV-2:*

The pathogen, SARS-CoV-2, induces COVID-19, and in the process of its infecting the host cell, it induces significant endoplasmic reticulum stress, which is the

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consequence of this endoplasmic reticulum commandeering by the pathogen for producing viral proteins. The heavy protein processing that might occur in the synthesis of the spike protein and other viral proteins in the endoplasmic reticulum may be too heavy an overload, leading to misfolding and activation of the UPR. The UPR aims to restore cellular balance through enhanced protein folding and removal of misfolded proteins. Chronic or extreme ER stress triggers inflammation, cellular malperformance, and apoptosis. Likewise, SARS-CoV-2 manipulates the UPR to evade immunity by blocking the induction of pro-apoptotic pathways and thus allowing itself to spread. It allows maintaining ER stress, thereby promoting the persistence of viruses within the host and enhancement of the inflammatory reactions associated with a lethal outcome in cases of COVID-19. This leads to the acceleration of tissue damage and cytokine storms. Thus, the SARS-CoV-2 link to ER stress is critical for viral pathogenesis and immune evasion [14–17].

- *Cytomegalovirus:*

The human cytomegalovirus, the agent of herpes, has evolved mechanism to escape the host defense. It generates large quantities of proteins that disrupts the MHC class I antigen-presentation pathway, thus avoiding T-cell recognition. The viral glycoprotein US6 interacts with the transporter associated with antigen processing gene (TAP) to block the movement of peptide into the ER additionally peptide storage into the molecules of MHC class I. Two endoplasmic reticulum-resident viral protein, US11 and US2, redirect class I MHC molecules immediately to the cytosol from the ER, in which both become deteriorated by the action on an enzyme known as proteasome [18–20].

The US3 protein of the human CMV takes on multiple roles in cells through its complex interactions. This includes preventing the presentation of the extracellular antigen that has been engulfed and processed for presentation by MHC class II molecules upon binding with HLA-DR by phagocytic cells, blocking he movement or transport of peptides to the ER, and associating transiently with peptide-loaded MHC class I molecules [21,22].

- *Hepatitis C Virus:*

Hepatitis C Virus replicates using the endoplasmic reticulum, which results in chronic endoplasmic reticulum stress. It causes biological responses that help it survive through inhibition of apoptosis and support for chronic infection. The amassing of the viral proteins in the ER greatly amplifies the tension, which in return causes inflammatory responses that end up damaging the liver. The creation and processing of viral proteins by ER-derived membranes promotes HCV survival in host cells by compromising ER function and inducing ER stress. The ER's calcium homeostasis is altered by HCV infection, which also results in oxidative stress that activates nuclear factor-κB and STAT3 [23,24].

- *RSV or Respiratory Syncytial Virus:*

RSV is one of the major antigens most pathogenic to infants, the elderly and immunocompromised adults. In the course of RSV infection, viral proteins build up inside the host cells, specifically in the ER, inducing the stress. Specifically, he virus utilizes the ER for protein production as well as folding that creates viral proteins beyond the ability of the ER to properly process. This induces the UPR, a cellular stress responds that aids in restoring the homeostasis in the ER.

The UPR may augment viral replication by repressing apoptosis and improving protein folding; however, chronic ER stress may result in cellular dysfunction, inflammation, and immunological escape. RSV-induced ER stress increases the inflammatory response classically seen with infection, most prominently in the lungs, and correlates with disease severity. RSV acts by modifying the ER stress pathways; this way, while it facilitates replication and survival within host cells, it heightens inflammatory damage to respiratory tissues, so that the pathogenesis of RSV infection is underlined by such a complex balance between viral replication and responses to the host [25–27].

III. ENDOPLASMIC RETICULUM STRESS IN BACTERIAL PULMONARY INFECTIONS

Chlamydia, *Salmonella*, and *Mycobacterium tuberculosis* were selected because each of these organisms has been demonstrated to interact with the host cell's endoplasmic reticulum, particularly how they take control of the machinery of the host cell to increase their probabilities of survival and multiplication. These are intracellular bacteria that have evolved for the endoplasmic reticulum as a source of replicative niches or manipulate the host cell response to increase its survival. These pathogens have been focused on, particularly in ER stress research, because they differ from each other in modes of infection, have specific functions for the ER at different times in their life cycles, and are directly related to human disease.

- *Chlamydia:*

Chlamydia trachomatis is one of the well-documented bacterial pathogens concerning human health, especially its role concerning sexually transmitted infections. The literature has more recently focused on how Chlamydia interacts with host cell processes. For example, it has been demonstrated that the bacterium triggers ER stress within the host cells. This interference in the host cell processes forms part of the survival strategy of the bacterium to create an intracellular environment amenable for replication. Chlamydia can further cause a halt in normal cellular processes, such as folding and processing of proteins. Once this occurs, the proper functioning of the ER can lead to ER stress that could be something the bacteria may use for enhancing survival by reprogramming normal host cell functions to their advantage. Activation of pathways, such as the UPR, is often linked to chlamydial infections, meaning that the cell can react to the increased load of the misfolded proteins. However, it may be used by Chlamydia as support for Chlamydia replication and survival. Interaction between Chlamydia and ER stress pathways may also underlie chronic inflammation typical in the infected tissues [28,29].

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➢ *Salmonella:*

Salmonella enterica, particularly, modified host cellular mechanisms with the induction of ER stress contributes significantly to *Salmonella* infections. *Salmonella* elicits inflammatory responses and modifies cellular stress pathways after entering host cells. *Salmonella* exploited its T3SS to alter the endoplasmic reticulum by injecting specific effector proteins directly into host cells. These effectors could influence cellular processes that are involved with the ER stress response. Cell response to endoplasmic reticulum stress is an important reaction to metabolic disturbances, and this disruption represents the rationale for the intervention by *Salmonella* as it attempts to alter normal cellular activities. Infection by these bacteria can utilize the autophagy pathways, particularly selective autophagy or xenophagy, to promote survival and contribute to host cell killing.

Salmonella sharply induces not only autophagy induced by nutritional starvation but also selective autophagy specifically aimed at and eliminating germs inside the host cell. In addition, the virulence factors released by *Salmonella* may help the latter escape from autophagic degradation through prevention of lysosomal fusion with autophagosomes, allowing germs to survive and multiply within host cells. These interactions emphasize the complex interplay between *Salmonella* and mechanisms of endoplasmic reticulum stress in infections [30,31].

➢ *Mycobacterium Tuberculosis:*

Mycobacterium tuberculosis (Mtb) is a major intracellular pathogen whose primary target cells are alveolar macrophages, representing the dominant immune cell type in the lungs. To withstand adverse conditions such as oxidative stress and nutrient starvation, the pathogen disrupts host cellular processes, for example by causing ER stress, and interferes with other cell functions, such as those related to phagosome formation and autophagy. It causes endoplasmic reticulum stress by disrupting the calcium homeostasis and promotes misfolding of proteins in the ER. This results in the activation of unfolded protein response, which Mtb manipulates for the host immune responses. Mtb can down-regulate pathways of pro-apoptosis while upregulating the signals of anti-inflammation to prevent killing by the host immune system. The bacterium's ability to evade immunity partly lies in its manipulation of cell death pathways, including apoptosis, necroptosis, and pyroptosis, which may be induced by the bacteria themselves inside the host during infection. It enhances survival and replication inside macrophages by inhibiting or modifying such pathways [32–34].

IV. THE ROLE OF ER IN MICROBIAL DEFENSE

All UPR signaling pathways, including those that promote apoptosis and provide protection, are activated in response to ER stress. On the other hand, ER stress will be extended and stressed cells will experience death if the protein level rises before equilibrium restoration. ER stress-associated degradation (ERAD), inflammation, autophagy and apoptosis are among the processes that may play the role in defense against pathogens in the ER.

➢ *ER Stress-Associated Degradation (ERAD):*

Endoplasmic reticulum-associated degradation (ERAD) is a major physiological pathway, representing a quality control of proteins inside the ER, which plays a role in identifying, retro-translocating and eliminating unassembled or misfolded protein gathering inside the endoplasmic reticulum. If the folding capacity of the endoplasmic reticulum is exceeded, especially during ER stress, a pathway, such as endoplasmic reticulum-associated degradation (ERAD), is activated to prevent harmful proteins from aggregating and possibly causing damage to the cell.The second stage involves the interaction of calnexin or calreticulin to misfolded proteins, which stops the transit of immature proteins to the Golgi apparatus. This stage encompasses the refolding of misfolded proteins. In step three, the endoplasmic reticulum (ER) channel designated as the Sec61p pathway-which facilitates the import of developing polypeptides and is implicated in protein translocation-transports misfolded proteins to the cytoplasm. Upon undergoing polyubiquitination and deglycosylation in the cytoplasm, the 26S proteasome-which catalyzes the bulk of protein degradation in developing mammalian cells-degrades them.

➢ *Inflammatory Reactions:*

Inflammation is a key component of the immune response to infection, marked by the activation of immune cells and production of cytokines. The inflammatory response and the host immune system effectiveness can be impacted by ER stress and ER signaling pathway activation. There are several pathways that link the type and length of the immune response. Hyper-inflammatory reactions and spontaneous inflammation can result from mutations in the ER-stress response pathway or protein folding [9,35]. NF-κB signaling is activated by ER stress and is thought to be a mechanism for triggering inflammatory responses. Immunogenicity regulation is another function of ER-stress pathways. By activating UPR transcription factors like XBP1s, ATF6 and CREBH, ER stress triggers inflammatory reactions. Through their interaction with canonical cytokine-regulatory transcription factors, UPR components trigger inflammatory signaling cascades in response to ER stress. The UPR may have a role in inflammatory illnesses, as shown by the increased production of pro-inflammatory cytokines after ER stress.

➢ *Autophagy:*

There are three different kinds of autophagy: chaperone-mediated autophagy, microautophagy, and macroautophagy. Here, the notion of "autophagy" mainly refers to macroautophagy. An expanded ER membrane enhances the synthesis of autophagosomes under ER stress. When misfolded proteins build up, stress is generated, this triggers the UPR to express proteins and chaperones that aid in the ER’s healing process. In response to stressors, eukaryotic cells have developed coping mechanisms. Involved in maintaining cellular homeostasis, autophagy is a fundamental process that has evolved to be preserved. It accomplishes this by assisting in the lysosomal degradation

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pathway, which regenerates and removes intracellular dead macromolecules and organelles. By regulating Ca2+, the IRE1α, PERK and ATF6α signaling pathways, ER stress promotes process of both inhibition and autophagy induction, serving dual functions. While pathological ER stress can cause autophagy to be inhibited, autophagy typically functions as a protective stress response that helps maintain cell survival during physiological ER stress.

- *Apoptosis:*

Apoptosis, the last kind of ER stress response, eliminates harmed cells by starting the apoptotic process. CHOP, a member of the C/EBP family, controls this mechanism, which in turn is controlled by molecules in its higher signal cascade. Apoptosis is facilitated by overexpression of CHOP, but CHOP deletion cells are resistant to it. In cases of intense ER stress, apoptosis is triggered through the caspase-12 and c-Jun N terminal kinases (JNK pathways. PERK,ATF6 and IRE1 regulates the apoptotic pathway in response to ER stress [36,37].

V. THE RESPONSE OF UNFOLDED PROTEINS

The endoplasmic reticulum (ER) of a cell is capable of sensing the amount of unfolded protein in its lumen. When the concentration exceeds a threshold, ER sensors activate the ER signal transduction pathway. This triggers a series of events knows as unfolded protein responses, leading to accumulation in the ER lumen and numerous physiological disruptions that hinder proper protein folding. The UPR is an evolutionarily conserved cellular response, facilitated by the three transmembrane proteins located in the ER: IRE1, ATF6 and PERK. Cold-shock proteins (csp) are the most prevalent of these proteins with sensor functions in their ER-luminal domains and response-initiating functions carried out by their cytosolic regions. When the sensors are turned on, a complex reply is sent back with the purpose of (i) down regulation of protein synthesis to avoid staking of unfolded proteins; (ii) up regulation of unfolded protein degradation protein; and (iii) enhancement of the capacity of proteins within the ER fold [38,39].

- *Disorders and Ailments Brought on by the ER's Metabolic Disturbance*

Lung disorders are frequently caused by ER stress, and one possible core unifying mechanism for many diseases might be protein-misfolding events. Misfolded proteins can become trapped in the ER by genetic mutations, and common diseases such as bacterial and viral infections can also cause ER stress. The loss of chaperones and folding molecules in the ER associated with aging may also lead to increased ER stress, underscoring the significance of protein-misfolding events in the lung health.

- *COVID-19*

In cultured cells transduced with SARS-CoV or cells that have overexpression of SARS-CoVS2 subunit, the expression of GRP78 and GRP94 (ER stress related gene) was also increased [40]. Phosphorylation of PRK and PERK is clearly evident in SAR-CoV-infected cells, which is similar to the case with GRP. Nevertheless, SARS-CoV is the cause of eIF2 phosphorylation because of SARS-CoV and does not respond to the antiviral functions of PERK and PKR in vitro [41]. Thus, understanding the state of the ER under UPR stress is essential for the elucidation of the complicated problem of corona virus-host interaction. On the other hand, if SARS-CoV accessory protein 3a promotes the expression of ATF4 and CHOP promoter activities then PERK will be activated.

Focusing on IRE-1 and its further outcomes, corona virus-infected cells spliced xbp1 mRNA very intensively, but not on the protein level. This may well be because of translation attenuation due to virus-induced eIF2 phosphorylation that prevents XBP1 protein from translating. In SARS, the corona virus' accessory viral protein (SARS-CoV) acts on the ATF6 domain and is cleaved. The ER retained ATF6 cleaved DNA-binding domains and transcription activation domains are transferred to the nucleus. Based on the results presented herein, it is possible to examine the evidence in favor of a direct viral interference with UPR through the use of one or several viral proteins. They suggested that UPR induction could accustom alter the host's antiviral reaction and is one of the checking off parts of corona virus-host interaction.

- *Influenza*

The synthesis of viral glycoproteins during infections can overburden ER protein folding machinery of infected host cell. This is countered by the host cell enhancing endoplasmic reticulum companion and diminishing transformation. The UPR may cause viruses to ripple other glycosylated proteins. Subsequent work demonstrated that viruses might have some sort of immunodeterrent to minimize the unavoidable incidence of ER stress to an extent that offered benefit to the viral mass. Human pathogen causing influenza-A virus (IAV) was used to determine the first threshold that triggers ER stress and UPR. Next, they found that it was not the HA, but the NA that was responsible for ER stress. IAV alleviates ER stress by producing the NS1 (non-structural proteins 1). NS1 suppressed the host mRNA processing factor CPSF30, subsequently inhibiting ER stress response elements like XBP1. This in vivo replication of the virus is closely linked to NS1's ability to suppress the development of ER stress. Nevertheless, the end result reflects the fact that IAV effectively controls folding capabilities to maximize glycoprotein yields are illustrated after a sequence of tests, including RT-PCR and splicing various portions of mRNA sequences of various strains of the influenza virus.

- *Tuberculosis*

The extracellular pathogen *Mycobacterium tuberculosis*, which was causing TB, possessed an exclusive structure called myco-membrane. When alveolar macrophages are infected by *M. tuberculosis*, a secretion system known as ESX-1 type-VII (T7SS) plays a critical role in the prevention of phagosome formation and the liberation of bacteria in the cytosol [42]. Despite the ability of *M. tuberculosis* to grow in the cytosol of the host, it induces significant ER stress that ultimately leads to host cell death. As for ER stress it is logical to assume that *M. tuberculosis* infection itself contributes to its development most of all, since it leads to a dramatic rise in intracellular Ca^{2+} levels and

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productions of ROS (reactive oxygen species). This is due at least to the T7SS protein ESAT6, which is necessary for the lysis of the phagosome however also, contributes to an augmentation of intracellular Ca^{2+} and ROS production. The Rav0297 coordinates itself to the ER as it is an effector protein and evokes intracellular Ca^{2+} and ROS to induce ER stress by its PGRS domain. Since, *M. tuberculosis* induces severe ER stress, to buffer this effect two ER localized chaperons BiP and calreticulin are transported through unconventional secretion pathway to plasma membrane. These “leaky” chaperones can thus also function as auto-antigens and pro-inflammatory signals as the host becomes infected [43]. To eliminate bacteria while avoiding the need for CHOP-mediated intrinsic apoptosis, extracellular calreticulin has been demonstrated to target at the CXCR1/TNFR1 receptor complex and activate the extrinsic apoptotic pathway. According to all the available data, the UPR that inhibits bacterial replication at this stage of infection by inducing apoptosis is a predominantly protective response to *M. tuberculosis* infection. Nonetheless, through promotion of germs in the advanced prosecution of the disease, apoptosis may also be root to disease.

- *Typhoid Fever*

The Gram-negative intracellular bacteria *Salmonella enterica* is the cause of typhoid fever as well as a multitude of gastrointestinal illnesses. *Salmonella* translocates diverse effector proteins through two T3SSs into the host cell to undergo intracellular replication. When *Salmonella* infects epithelial cells it triggers the UPR which is seen to enhance the survival of bacteria. A recent study reveals that SlrP, a effector protein T3SS, resides within the lumen of ER and binds to ERdj3, a co-chaperone Hsp40/DnaJ that is essential for proper functioning of BiP [44]. SlrP is usually expected to lead to protein misfolding in the endoplasmic reticulum lumen and activates the UPR during pathogenicity, although it hasn’t studied yet. More work therefore is thus still needed to fully appreciate how *Salmonella* engages with UPR signaling and ER stress and the effects on the immunological responses.

VI. THE INVOLVEMENT OF VIRUSES AND BACTERIA INFECTION IN ENDOPLASMIC RETICULUM IN THE PULMONARY PATHWAY

➢ *Viral Infection*

Viruses use the host immunity in order dodge the immunological responses. They also can engage with the host’s unfolded protein responses to establish optimal conditions for the inception of chronic affliction. In fact, viral infections can trigger stress in the ER. Rather than defending against infection, UPR and ER stress have been demonstrated to enhance the hepatitis B virus replication. Endoplasmic replication is usually caused by a range of viruses, such as RSV, influenza-A virus, SARS-CoV-1 and 2 (main causing organism for COVID-19 and SARS, respectively). The mechanism of virus-induced ER stress may result from viral protein translation exceeding the protein folding capacity. IAV has been shown to cause inflammation and death in primary human bronchial epithelial cells by activating IRE1 while only weakly activating PERK or ATF6 [45,46].

- *The Mechanism of Viral Infection in Pulmonary Pathway*

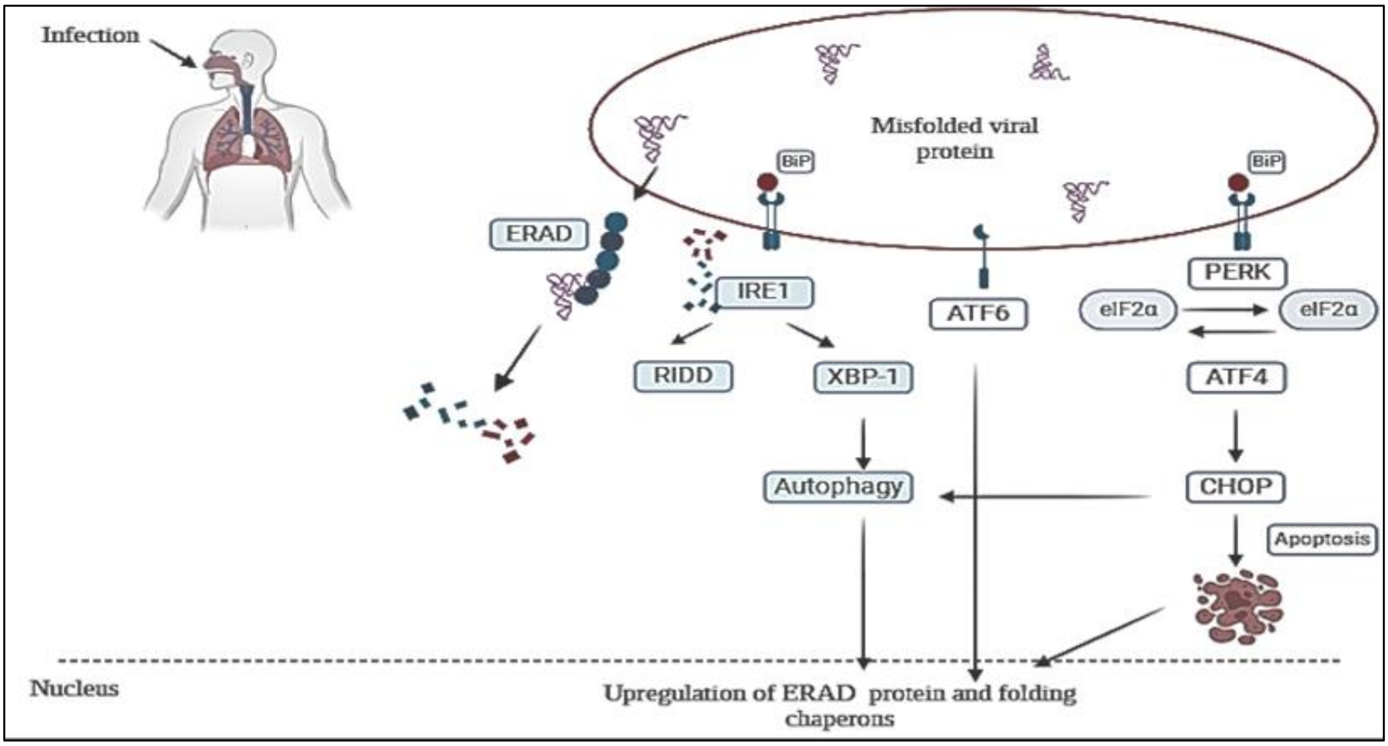

Fig 1 Mechanism of Viral Infection on Endoplasmic Reticulum

A vital component of the host's antiviral defense is the PERK pathway. Viral replication may be controlled by PERK-mediated eIF2α phosphorylation. Controlling eIF2α phosphorylation is essential for enveloped virus survival,

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such as the HSV (herpes simplex virus). By enhancing ER-associated degradation (ERAD), which inhibits the immune response, HSV reduces MHC-I levels. Following an infection with HIV-1, ERAD destroys CD4 protein. To lessen ER stress and load, *regulated Ire1 dependent decay* (RIDD) breaks down mRNAs [47,48].

Despite the fact it is unclear if RIDD enactment is beneficial for all viral infectivity, RIDD is directly associated to the viral RNA amalgamation. Typically likely because infection replication requires large amounts of membrane proteins and lipids, which are produced within the ER [49]. Apoptosis may transpire if the build-up of unfolded proteins is beyond the endoplasmic reticulum's carrying capability. In response to the stress of ER, the initiation of CHOP leads to the promotion of cell death since one of its main functions is to prevent RNA viruses from infecting host cells. Although the downstream targets of CHOP are yet unclear, a route that depletes intracellular glutathione, reduces Bcl-2 expression, and increases free radicals has been linked to CHOP-mediated death. During an infectious bronchitis virus infection, IRE1 is purportedly necessary for the activation of autophagy [36].

➢ *Bacterial Infection*

Cell damage caused by bacterial infection is frequently characterized by loss of cellular integrity and cell death. The UPR can be selectively triggered by bacterial infection and toll-like receptor (TLR) activation. For instance, to encourage the release of inflammatory mediators, TLR2 and TLR4 selectively activated IRE1 (Inositol-requiring enzyme 1). The UPR can also be undermined by respiratory infections [50]. For example, the intracellular bacterium *Chlamydia*, which multiplies in an ER-associated compartment, specifically prevents the IRE1 pathway from being activated. Bacterial toxins secreted into the environment have the ability to alter the UPR. In human primary airway cells, for instance, pyocyanin (derived from *Pseudomonas aeruginosa*) induced this response as shown by XBP1(X-box binding protein 1) splicing and the stimulation of BiP (Binding immunoglobulin Protein) [51,52].

- *The Mechanism of Bacterial Infection in Pulmonary Pathway*

There are several virulence factors that bacteria have developed that cause the activation of UPR. A well-known instance is the endotoxin lipopolysaccharide (LPS), which is found in the outer membrane of Gram-negative bacteria. Heat shock protein 90 kDa beta member 1 i.e., Grp94 (Glucose regulated Protein 94), an ER chaperone, transports LPS from the ER to the plasma membrane where it is recognized by toll-like receptor 4 (TLR4). Following LPS treatment, TLR4 and Grp94 expression rises. But because Grp94 expresses itself at a lower level than TLR4, folding and plasma membrane translocation of TLR4 are insufficient.

By releasing substances that can penetrate the ER lumen, other bacteria have developed defense mechanisms to trigger UPR. Among these is tunicamycin, an inhibitor of N-linked glycosylation of proteins that is frequently employed as a positive control to induce UPR [52,53].

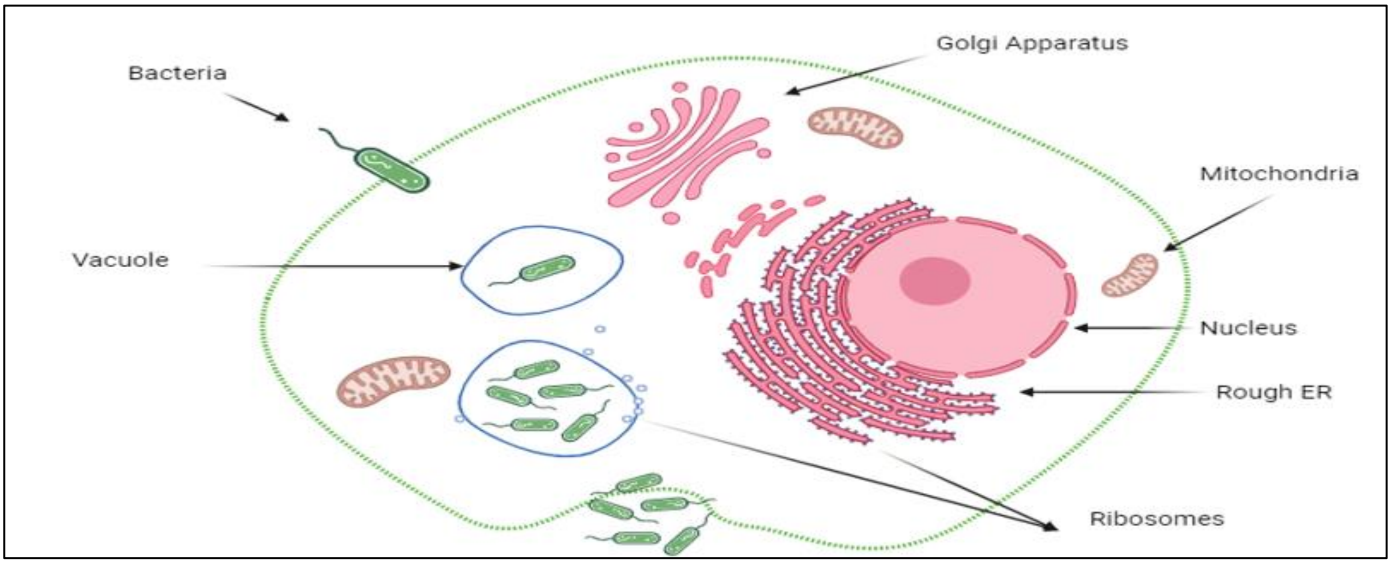

Fig 2 Mechanism of Bacterial Infection on Endoplasmic Reticulum

VII. METHODOLOGY

The broad category of illnesses known as respiratory diseases affects the complex and essential mechanism that gives us our breath. The good news is that preemptive actions and procedures can avoid a large number of respiratory illnesses.

➢ *Tracheostomy*

For patients in severe condition who need extended mechanical ventilation for airway problems and acute respiratory failure, tracheostomy is an essential surgical treatment. Access to the tracheobronchial tree, a passageway that transports warm, moist air to the lungs and allows them to release phlegm and carbon dioxide, is the issue that this article attempts to address. When there is upper airway blockage, a tracheostomy offers a low-resistance route for air

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exchange. During the surgery, the front of the neck is made accessible to allow for the insertion of a breathing tube via the opening. When a patient has an upper airway obstruction or requires a ventilator for several weeks, this is frequently required. Following the front lower neck incision, the windpipe is cut, and the tube is inserted using Velcro, surgical tape, or sutures.

➢ *Transplantation*

Patients with diseases such as pulmonary hypertension, cystic fibrosis, pulmonary fibrosis, idiopathic pulmonary fibrosis, and Sarcoidosis may be candidates for lung transplant therapy. They enhance quality of life by substituting unhealthy or polluted lungs for healthy ones. During the procedure, anesthesia is administered, and the veins of the patient are connected to the healthy donor lung. Immunosuppressive medications are necessary for patients to survive throughout their 3 to 4 week recovery period. Other critical lifestyle decisions include keeping oneself clean, getting vaccinated annually, and choosing foods that promote heart health.

➢ *Oxygen treatment or therapy*

To maintain appropriate blood oxygen levels, supplemental oxygen treatment is crucial for those with respiratory conditions such as COPD, COVID-19, emphysema, and sleep apnea. Low oxygen levels are potentially fatal and can harm organs. Trachea tubes, nose tubes, and face masks can all be used for oxygen treatment. It can be administered at a hospital or at home, and side effects include headaches, exhaustion, and bloody or dry nose. In general, oxygen treatment is safe and effective in treating a number of conditions, including as RDS, asthma, COPD, heart disease, and pneumonia.

➢ *Thoracentesis*

In order to facilitate breathing, a treatment known as thoracentesis is used to drain extra fluids from the pleural cavities. A doctor will usually require 10 to 15 minutes to do the procedure, which entails putting a needle between the ribs and into the pleural area. Coughing or chest discomforts are possible side effects of the surgery for patients. After the needle is taken out, the area is bandaged. To aid with treatment planning, the fluid collected is sent for laboratory test to identify pleural effusion. It could be necessary to order a chest X-ray to look for lung issues. Thoracentesis side effects might include discomfort, bleeding, bruises, infection, or pneumothorax.

VIII. RESULT AND DISCUSSION

Studies show that lung diseases are exacerbated by ER stress, and some lung diseases are linked to mutations affecting the UPR molecule, ER chaperones, misfolded proteins, and metabolisms. Proteostasis has to be maintained for good lung function since ER stress impacts pulmonary disease homeostasis through misfolded protein accumulation, epigenetic changes, and decreased autophagy.

As per our research, individuals with weakened immune systems are more susceptible to bacterial and viral infections, particularly those who are taking medicine for conditions like COPD, cancer, and other ailments. Lung illnesses are mostly caused by smoking or breathing in environmental contaminants and pathogens; personal hygiene comes in second. The rapid advancements of modern society have led to a rise in various illnesses, stemming from factors such as pollution and inadequate personal hygiene. It is stated that males are typically more vulnerable to bacterial illnesses, although viral and bacterial infections are neither gender or sexually dimorphic, meaning they can affect both sexes equally.

IX. CONCLUSION

In simple words, endoplasmic reticulum stress plays a key role in both viral and bacterial lung infections, thus it influences the outcome of the immune responses and ailment consequences. In this case, pathogens that include respiratory viruses such as RSV and SARS-CoV-2 and bacteria such as *Mycobacterium* and *Salmonella* can produce ER stress by the initiating the UPR following infection. This stress response activates only immunological signaling pathways, thereby strengthening inflammation and the activation of the immune response. Established or chronic ER stress might incorporate immunological dysfunction to prevent immunity or ensure chronic infection or lead to tissue damage. Potentially involved in the pathogenesis of ER stress in pulmonary infections are those strategies that can restore ER homeostasis, reduce inflammation, and augment host's capacity for defense against pathogens.

Selected idiopathic and secondary respiratory disease patients and their relevant animal models exhibit active UPR in airway cells. The development and aggravation of pulmonary fibrosis have been associated with ER stress. Furthermore, a growing body of information supports the premise that ER stress participates in the development of obstructive lung disorders, such as asthma, pulmonary infections like cystic fibrosis and specific viral infections, and lung neoplasms. While a number of small-molecule inhibitors is employed in studying the UPR in models of illness, products that has this teamed of properties has been noted to exhibit complicated side effects that may include off target interactions, which may still need genetic manipulation to confirm their effect. While the mechanisms connecting these processes, in particular cases of diseases, remain unknown there is evidence that excessive UPR activation may be implicated in the development and progression of diseases. UPR is an attractive candidate for the other potential therapeutic strategies in the future due to its role in regulating ER stress and modulation of the spectrum of respiratory diseases.

Further research is needed to comprehend the role of ER stress in lung diseases and health. Merely seeing ER stress characteristics in the pulmonary pathway is insufficient. A more comprehensive investigation is required to fully grasp the molecular mechanism of ER stress and evaluate the safety of UPR therapies in pulmonary illnesses. A deeper comprehension of parasite relationships and cellular stress responses, specifically UPR, may make it feasible to pinpoint

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new therapeutic targets for ER stress or specific UPR branches. This could lead to more effective approaches to treating pharmacological resistance or treatment toxicity associated with currently available therapies. It is also possible to leverage differences in UPR networks between hosts and parasites against them.

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