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Endoplasmic Reticulum Stress Interacts With Inflammation in Human Diseases

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The endoplasmic reticulum (ER) is a critical organelle for normal cell function and homeostasis. Disturbance in the protein folding process in the ER, termed ER stress, leads to the activation of unfolded protein response (UPR) that encompasses a complex network of intracellular signaling pathways. The UPR can either restore ER homeostasis or activate pro-apoptotic pathways depending on the type of insults, intensity and duration of the stress, and cell types. ER stress and the UPR have recently been linked to inflammation in a variety of human pathologies including autoimmune, infectious, neurodegenerative, and metabolic disorders. In the cell, ER stress and inflammatory signaling share extensive regulators and effectors in a broad spectrum of biological processes. In spite of different etiologies, the two signaling pathways have been shown to form a vicious cycle in exacerbating cellular dysfunction and causing apoptosis in many cells and tissues. However, the interaction between ER stress and inflammation in many of these diseases remains poorly understood. Further understanding of the biochemistry, cell biology, and physiology may enable the development of novel therapies that spontaneously target these pathogenic pathways.

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The endoplasmic reticulum (ER) is a membrane-bound organelle that plays a crucial role in many cellular processes, in particular, the folding and trafficking of secretory and membrane proteins, lipid and carbohydrate metabolism, and detoxification. ER protein folding and transport are highly sensitive to any disturbance in ER homeostasis. One such disturbance, termed ER stress, involves the accumulation of unfolded and misfolded proteins, and activates the unfolded protein response (UPR), which recruits downstream signaling pathways to restore ER homeostasis. In the presence of ER stress in mammalian cells, UPR is activated via three branches of signaling pathways, each involving a protein sensor on the ER membrane: inositol-requiring kinase 1 α (IRE1α), pancreatic ER eIF2α kinase (PERK), and activating transcription factor 6 α (ATF6α). In the absence of ER stress, ER luminal-binding protein chaperone BiP/GRP78 maintains the inactive states of these three pathways by binding to the luminal domains of these sensors and prevents their activation. In ER stress, BiP dissociates from the luminal domains, thereby activating these three branches of UPR (Cao and Kaufman, 2012; Hetz, 2012).

The most conserved signaling branch of UPR involves IRE1, a type I transmembrane protein with both a Ser/Thr kinase domain and an endoribonuclease (RNase) domain in its cystolic portion. Upon release from BiP inhibition, the luminal domain of IRE1α undergoes homo-oligomerization and *trans*-autophosphorylation, and initiates its kinase and RNase activities. The endoribonuclease activity of IRE1α cleaves and removes a 26 base intron from the mRNA of the X-box-binding protein-1 (XBP1) and produces a translational frame-shift that produces the active CREB/ATF base leucine zipper-containing (bZIP) transcriptional factor XBP1s. XBP1s is a crucial transcriptional activator of many UPR genes that produce proteins and chaperones to regulate ER protein folding and trafficking, phospholipid biosynthesis, ER membrane expansion, and ER-associated protein degradation (ERAD). Several recent studies have implicated the IRE1α-XBP1 pathway to be at the intersection of several molecular pathways in response to cellular stress. One pathway involves the kinase domain of IRE1α which binds with TNFα receptor-associated factor 2 (TRAF2) in the cytoplasm, leading to TRAF2 phosphorylation and subsequent activation of the NF-κB and c-Jun N terminal kinase (JNK) pathways, thereby contributing to inflammatory and pro-apoptotic signaling in the cell (Walter and Ron, 2011). Another pathway involves the binding of IRE1 α to pro-apoptotic proteins Bax and Bak on the mitochondrial outer membrane which leads to mitochondrion-dependent cell death. Previously, XBP1 was the only known substrate of IRE1α. Interestingly, during ER stress, the endoribonuclease domain of IRE1α was recently found to target a subset of ER-localized mRNAs, which are subsequently degraded in a process called regulated IRE1-dependent decay (RIDD), a mechanism that further relieves ER stress (Tabas and Ron, 2011). In addition, RIDD has recently been linked to the translational activation of retinoic acid-inducible gene I (RIG-1), thereby causing a cell-autologous NF-κB-mediated inflammatory response that amplify the immune response against RNA viruses (Lencer et al., 2015). This IRE1α-RIDD-RIG1 pathway suggests an important role for ER stress in immune surveillance and microbial stress response.

Another branch of the UPR signaling involves the PERK, also a type I transmembrane protein with a Ser/Thr kinase domain in its cystolic portion. Upon release from BiP inhibition in response to ER stress, PERK becomes activated in a process similar to IRE1α activation. Activated PERK phosphorylates the Ser51 of the α subunit of eukaryotic translation initiation factor 2 (eIF2α), which competes with eIF2B and reduces the rate of protein translation, thereby resulting in reduced global protein synthesis and a subsequent reduction ER protein-folding load.

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In addition to inhibiting global protein synthesis, eIF2α also plays a unique role in selectively promoting the translation of a subset of mRNAs, in particular, the mRNA encoding a bZIP transcription factor ATF4. ATF4 is a key player in several stress-response pathways and induces the expression of UPR-associated inflammatory signaling molecules, ER chaperones and trafficking machinery, antioxidative stress responses, and autophagy. A downstream target of ATF4 is CCAAT/enhancer-binding protein homologous protein (CHOP), which promotes oxidative stress and apoptosis through multiple downstream pathways including ER oxidase 1α, and Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII). CHOP has also linked to pro-survival protein Bcl-2, pro-apoptotic factors Bim, telomere repeat binding factor 3, and death receptor 5 (Lu et al., 2014).

The third branch of the UPR involves the ATF6α pathway. ATF6α is a type II transmembrane protein with a CREB/ATF bZIP domain at its N-terminal cytoplasmic portion and belongs to the family of regulated intramembrane proteolysis (RIP)-regulated bZIP transcription factors. Upon dissociation from BiP in response to ER stress, ATF6α travels to the Golgi apparatus where it cleaved in its luminal domain and transmembrane region by site-1-protease (S1P) and S2P, respectively. This releases a free cystolic fragment p50 that migrates to the nucleus and activated ATF6α subsequently stimulates the expression of ER chaperones, transcription factors, the components of ERAD, and ER biogenesis. Dysfunction of ATF6α pathway has been implicated in a variety of disease pathologies. Recently, *ATF6*α mutations that attenuate its transcriptional activity in response to ER stress are associated with foveal hypoplasia and implicated in achromatopsia, a condition characterized by color blindness and reduced visual acuity (Kohl et al., 2015). Other RIP-regulated bZIP transcription factors including CREBH and OASIS, and Luman play important and diverse roles in different tissues (Cao and Kaufman, 2014).

Infection and Autoimmunity

The presence of ER stress has been reported in both autoimmune diseases and infections. Autoimmune diseases such as systemic lupus erythematous (SLE), inflammatory bowel disease (IBD), primary biliary cirrhosis (PBC), and autoimmune-mediated arthritis have been associated with ER stress and the UPR, which may play a significant role in modulating the course and outcome of the pathological states. A study published in 2014 quantified mRNA expression of ER stress markers such as IRE1α, XBP1, CHOP, and PERK in 76 patients with SLE disease activity and found that IRE1, PERK, and CHOP mRNA transcripts were downregulated in SLE patients while total XBP1, XBP1s, and mesencephalic astrocyte-derived neurotrophic factor (an ER stress-induced cytoprotective protein) were upregulated (Petrova et al., 2003; Wang et al., 2014). Another study published in 2010 used a two-hybrid screen in the cDNA library of a patient with lupus nephritis, using an O-81 single-chain Fv as bait. An alternative splice variant of the homocysteine-induced ER protein (Herp) transcript was discovered to exhibit moderate binding to the O-81 mAb, and immunization with the HERP protein was necessary for formation of anti-dsDNA antibodies even with the presence of oligonucleosome antigens (Hirabayashi et al., 2010). Lee et al. (2015) found that, in response to ER stress inducer thapsigargin, levels of IRE1, ATF6, PERK, and p-eIF2α decreased in T lymphocytes of lupus patients compared to those of normal controls, while pro-apoptotic molecules Bax and caspase 6 were elevated in patients with SLE. In the IBD field, deletion of *Xbp1* in intestinal epithelial cells of mice led to histological findings of IBD, symptoms of enteritis, and increased signs of ER stress (Kaser et al., 2008). In IBD patients, XBP1 SNPs rs5997391, rs5762795, and rs35873774 were found to be strongly associated with IBD (Kaser et al., 2010). Both p-eIF2α and one of its cytosolic kinases dsRNA-activated protein kinase (PKR) in colonic epithelial cells are protective against chemical-induced colitis by inducing protective UPR signaling including ER chaperones (Siyan et al., 2012; Cao and Kaufman, 2013a; Cao et al., 2014). Interestingly, p-eIF2α, but not PKR, is required for the secretory function of Paneth cells in the small intestine by inducing ER chaperones, transcription factors, ERAD machinery, and autophagy. The expression of a non-phosphorylatable *eIF2*α in intestinal epithelial cells increased the susceptibility of mice to salmonella infection and chemical-induced colitis (Cao et al., 2014). The protective role of ER chaperone response in intestinal epithelial cells upon mucosal inflammation was demonstrated using murine models with deletion of ER chaperone gene $P58^{IPK}$ and *Atf6*α, an transcriptional activator of multiple ER chaperone genes. Furthermore, chemical chaperones 4-phenylbutyrate (PBA) and tauroursodeoxycholate (TUDCA) were shown to alleviate intestinal inflammation in several murine models of IBD, by reducing ER stress and apoptosis in intestinal epithelial cells (Cao et al., 2013; Luo and Cao, 2015). Another study recently discovered that β-Arrestin2-mediated inflammation-induced colitis through positive regulation of p53-upregulated mediator of apoptosis (PUMA) activity in mice, and β-Arrestin2 was also upregulated in IBD patient intestinal tissue (Zeng et al., 2015). Anti-citrullinated antibody is a highly specific marker of rheumatoid arthritis, and anti-citrullinated calreticulin, an essential ER chaperone, is present in synovial tissue of joints and binds preferentially to the shared epitope domain of β1 domain of the HLA-DR found in RA patients (Ling et al., 2006,2013). An exome-sequencing study in five families with hereditary autoimmune disorders (including arthritis and interstitial lung disease) revealed mutations in coatomer protein complex, subunit α (COPA, known to mediate ER-Golgi vesicular transport as a vesicular coat protein). Additional experiments showed that defects in COPI vesicular transport leads to ER stress and an increased T helper 17 response and proliferation (Watkin et al., 2015). PBC lesions have deregulated autophagy and senescence in biliary epithelial cells, which is linked to increased ER stress (Sasaki et al., 2014). Although the functional role of ER stress in the pathogenesis of PBC is unknown. In patients with limited cutaneous systemic sclerosis, the expression of ER stress markers BiP, ATF4, ATF6, and XBP1s were relatively increased in peripheral blood mononuclear cells (Lenna et al., 2013). Anti-chaperone antibodies have been discovered in a number of autoimmune diseases, including inflammatory bowel disease, myasthenia gravis, RA, SLE, systemic sclerosis, primary biliary cirrhosis, juvenile autoimmune arthritis, and autoimmune hepatitis (Nagayama et al., 1994; Kreisel et al., 1999; Eggleton et al., 2000; Bodman-Smith et al., 2004; Watanabe et al., 2006; Goeb et al., 2009; Komurasaki et al., 2010; Tarr et al., 2010; Weber et al., 2010). However, the precise mechanism of how these antibodies are generated and how they contribute to the progression of the disease are still being studied. PERK was recently shown to be involved in initiating the JAK1-STAT3 pathway in microglia and astrocytes in neuroinflammation (Meares et al., 2014). In multiple sclerosis experimental models, mice with oligodendrocyte-specific knockout of *Perk* exhibit impaired UPR and exacerbated experimental autoimmune encephalopathy (EAE) (Hussien et al., 2014). Moreover, activation of PERK in oligodendrocytes was shown to confer resistance against EAE (Lin et al., 2013). Recent studies also linked ER stress to tumor immunity. ER chaperones BiP, gp96, and calreticulin were found on plasma membranes and may act as damage associate molecular patterns and activate immune responses. Release of BiP and gp96 into the extracellular matrix have been shown to induce

tumor immunity through CD8+ T-cells (Udono et al., 1994; Tamura et al., 2011). Immunity against fibrosarcoma can be attained by binding of extracellular gp96 to CD91, endocytosis of the chaperone-receptor complex, and presentation on MHC I and MHC II to CD4+ and CD8+ T-cells (Srivastava, 2002).

Infection with viruses, bacteria, or parasites has been shown to induce ER stress and activate the UPR. Envelope viruses program the cell to produce massive quantities of viral protein, including, e.g., the hemagglutinin protein of the influenza virus and the spike protein of SARS-CoV, causing ER stress and initiating the UPR (Watowich et al., 1991; Chan et al., 2006). Overexpression of IRE1α protected a non-small cell lung carcinoma cell line H2199 cells from avian coronavirus infectious bronchitis virus infection-induced apoptosis (Fung et al., 2014), whereas the deletion of XBP1, the downstream target of IRE1α in fibroblasts delayed propagation by murine cytomegalovirus (Drori et al., 2014). Knockout mice deficient in autophagy protein Map1-LC3b displayed increased expression of IL-17 and lung pathology upon infection with respiratory syncytial virus. Inhibiting IL-1 production abolished this phenotype, and knockdown of IRE1 inhibited production of IL-1β (Reed et al., 2015). The expression of BiP and Grp94 in coxsackievirus B3-induced myocarditis was increased and correlated with severity of symptoms. Upon induction of ER stress within cardiomyocytes, cardiac function was compromised and the myocarditis was exacerbated, potentially through elevated levels of inflammatory cytokines including IL-6, IL-12, TNFα, and MCP-1 (Zha et al., 2015). *Pseudomonas aeruginosa* infection complicates chronic lung diseases including cystic fibrosis and chronic obstructive pulmonary disease. A recent study showed that conditioned media containing *Pseudomonas* virulence factors pyocyanin and elastase and alkaline protease was sufficient to induce XBP1s, CHOP, BiP, and GADD34 expression in primary bronchial epithelial cells. The activation of most of the ER stress markers were dependent on TGFβ activated kinase-1 and p38 MAPK, except the induction of GADD34. Heme-regulated eIF2α kinase (HRI), instead of ER stress sensor PERK, was shown to induce the expression of GADD34, which plays a cytoprotective role in primary bronchial epithelial cells against *Pseudomonas* infection (van 't Wout et al., 2015). *Plasmodium burghei* infection also induces ER stress, which allowed hepatocytes to adopt radical metabolic changes during the infection. This metabolic shift was shown to help *Plasmodium burghei* establish successful infection, namely increasing their exoerythrocytic forms. The activation of XBP1s induces phosphotidylcholine synthesis, which has been shown to be beneficial for growth of the parasite (Inacio et al., 2015).

Metabolic Disease

Although sedentary lifestyles and excess caloric intake are considered culprits on the macroscopic scale for increases in rates of metabolic disorders including type 2 diabetes and obesity, recent scientific literature has shed light on the systems gone awry at the molecular level related to ER homeostasis (Cao and Kaufman, 2013b). In mammals, the liver is the master organ in regulating glucose metabolism. Insulin resistance in the liver promotes gluconeogenesis and lipogenesis, which contributes to subsequent hyperglycemia and hyperlipidemia (Cao and Kaufman, 2013b). In the setting of ER stress, insulin resistance develops through IRE1α-mediated activation of JNK and IKK, which subsequently inhibits insulin action by downstream serine phosphorylation of insulin receptor substrate (IRS) 1 and 2. In addition to IRE1α-mediated activation, JNK can be induced by CAMKII and eIF2α kinase PKR in the setting of ER stress to induce insulin resistance (Timmins et al., 2009). In addition to suppressing insulin action, ER stress may lead to downstream activation of transcription factors that are involved in liver gluconeogenesis and lipogenesis. Among these transcription factors is CREBH, a RIP-regulated bZIP transcription factor that contributes to the activation of gluconeogenic and inflammatory response genes. However, another pathway mediated by ATF6α suppresses gluconeogenesis via CREB-regulated transcription coactivator 2 (CRTC2) (Wang et al., 2009). Although several pathways intersect and are involved in insulin resistance in the liver, it remains an area of mystery how these pathways are regulated in response to different metabolic signals. In addition to glucose dysregulation, lipids can accumulate in the liver in the setting of ER stress which further contributes to insulin resistance. There is recent evidence to suggest that PPARβ/δ serves a protective role in insulin resistance via an AMPK-dependent signaling pathway (Salvado et al., 2014). However, the exact mechanisms and role players in insulin resistance remain controversial and much remains to be unearthed in future studies.

Type 2 diabetes is characterized by pancreatic β cell dysfunction against a background of chronic low-grade inflammation (Donath et al., 2005). Recent evidence demonstrates that ER stress and inflammation are critical contributors to impaired β cell homeostasis in the pathogenesis of type 2 diabetes. ER stress leads to inflammatory cytokine secretion, and these inflammatory cytokines, in particular IL23, IL24, and IL33, amplify ER stress in pancreatic β cells (Hasnain et al., 2014). Another cytokine IL1β, activated by NLRP3 inflammasome during ER stress, is also implicated in pancreatic inflammation and autophagy (Montane et al., 2014). The key molecule in this signaling cascade is thioredoxin-interacting protein (TXNIP) that links ER stress and inflammation in β cell pathology in a murine model of type 2 diabetes (Oslowski et al., 2012). TXNIP expression is induced by IRE1- and PERK-mediated pathways. TXNIP subsequently activates NLRP3 inflammasome and elevates IL1β secretion that causes pancreatic inflammation (Abderrazak et al., 2015). These data suggest that ER stress and inflammation form a vicious cycle in pancreatic β cell dysfunction in type 2 diabetes. Obesity involves a multifactorial disease process that leads to its development and maintenance. Recent studies suggest that activation of ER stress and NF-κB pathways in the hypothalamus impair leptin signaling, which predisposes the individual to diet-induced obesity (Ropelle et al., 2010; Williams, 2012; Zhou and Rui, 2013). Other studies propose a mechanistic approach that involves chronic excessive food intake leading to adipocyte hypertrophy as the source of ER stress, which was shown to initiate a pro-inflammatory state in adipose tissue and activate downstream metabolic pathways that promote insulin resistance. These adipocytes release MCP-1, M-CSF1, MIF to recruit macrophages that release additional MCPs and inflammatory cytokines, such as TNFα, IL6, IL1β, as well as initiate iNOS signaling, to stimulate inflammation (Schaffler and Scholmerich, 2010). Free fatty acids released by inflamed adipocytes induce Toll-like receptor 4 (TLR4) to further amplify insulin resistance and inflammation. The resultant increase in serum levels of fatty acids, lipids, and leptin, as well as decrease in adiponectin, promote lipid accumulation and lipotoxicity, creating a cycle that stimulates and maintains obesity (Ye et al., 2014).

Neurological Disease

Amyotrophic lateral sclerosis (ALS) is a debilitating neurological disease in which motor neurons are selectively lost in the motor cortex, spinal cord, and peripheral nervous system. Pathologically, ALS is characterized by gliosis replacing affected motor neurons. The volume of myelinated fibers in motor neurons is decreased, and the ventral nerve roots are thinned. Neuropathological findings often include intracellular

inclusions suggestive of impaired protein folding: ubiquitinated aggregates, TDP-43 aggregates (common in non-SOD1 ALS), and phosphorylated and nonphosphorylated neurofilament inclusions (Arisato et al., 2003). The majority of ALS cases are sporadic (sALS), but of the 5–10% of cases that are familial (fALS), 20% have been linked to mutations in Cu/Zn superoxide dismutase (SOD1) (Deng et al., 1993; Tobisawa et al., 2003a; Byrne et al., 2011). Over a hundred mutations within the *SOD1* gene have been discovered, the most studied of which is G93A, which was able to recapitulate the ALS phenotype in a G93A mSOD1 transgenic mouse. However, changes in the functionality of SOD1 have a poor correlation with disease severity and progression; rather, the ability of mSOD1 to form aggregates that localize to the ER is a strong indication of disease (Borchelt et al., 1994).

In 2003, Tobisawa et al. first demonstrated that mSOD1 physically associated with the ER membranes and was implicated in the ERAD pathway in the pathogenesis of ALS. Additionally, mSOD1 (L84V and H46R) transgenic mice displayed high expression of BiP prior to onset of symptoms of motor neuron degeneration. These results strongly suggested that the accumulation of mSOD1 potentially increased ER stress and activated the UPR (Tobisawa et al., 2003b). In 2006, another study showed that mSOD1 forms aggregates in the ER and interacts with BiP in spinal motor neurons of symptomatic G93A mSOD1 transgenic mice (Kikuchi et al., 2006). It was also found that ER stress markers PDI, p-eIF2α along with ATF6, IRE1, PERK, Erp57, BiP, and CHOP are upregulated in post-mortem spinal cord samples of human patients with sporadic ALS (Atkin et al., 2008).

Motor neurons in ALS patients undergo apoptosis, leading to the classical symptoms of motor dysfunction and paralysis. Spinal cords of ALS patients possess activated caspase-1, caspase-3, and caspase-9 and decreased levels of Bcl-2 (Pasinelli et al., 2000; Guegn et al., 2001; Inoue et al., 2003). Overexpression of Bcl-2 in transgenic mSOD1 mouse models slows onset of the disease (Kostic et al., 1997). Persistent ER stress, through IRE1α, can induce apoptosis via cleavage and activation of caspase 12, an upstream activator of the apoptotic pathway. Interestingly, deletion of *Xbp1*, the downstream target of IRE1α, ameliorates mSOD1 aggregation and toxicity in both NSC34 motor neuron cell lines and G86R mSOD1 transgenic mice. In fact, lifespan is increased in XBP1-deficient G86R mSOD1 mice compared to transgenic mice with endogenous levels of XBP1, presumably through shunting towards the autophagy pathway rather than the UPR (Hetz et al., 2009). A 2004 study by Wootz et al. (2004) demonstrated that in the transgenic G93A mSOD1 mouse model of ALS, caspase-12 is cleaved during early stages of the disease, with high procaspase-12 turnover rates (as evidenced by high mRNA levels but low protein expression). Kieran et al. (2007) showed that BH3-only protein p53-upregulated mediator of apoptosis (PUMA) expression coincided with an increase CHOP levels, which are thought to mediate the transition from pro-survival to pro-apoptosis. Moreover, abrogation of Puma expression in mSOD1 G93A mice delayed onset of symptoms and slowed progression of disease without extending lifespan. Another apoptotic pathway may occur through Apoptosis signal-regulating kinase 1 (ASK1), in which ASK1 and TRAF2 are recruited by IRE1 to the ER membrane surface and then activated. Nishitoh et al. in 2008 reported that mSOD1 inhibited ERAD and induced ER stress by interacting with Derlin-1 and thus activating the ER stress-ASK1 apoptotic pathway. Ablating ASK1 expression extended lifespan of G93A mSOD1 mice and delayed progression of disease with no significant difference in age of onset of symptoms (Nishitoh et al., 2008). However, it remains unknown how mSOD1 regulates Derlin-1 and ERAD in the dysfunction and apoptosis of motor neurons.

The reason behind why motor neurons are specifically affected in ALS still is largely unknown. It was postulated that the synthesis of large amounts of proteins aided in triggering ER stress and that motor neurons were especially sensitive to their continual production of neurotransmitters. In 2008, Saxena et al. discovered that certain subtypes of motor neurons were more resistant to ER stress, specifically fast fatigue-resistant and slow motor neurons. Neurons that were sensitive to ER stress were fast fatiguable, and treatment with salubrinal, an ER stress protective agent, attenuated disease progression after onset of symptoms and extended the lifespan of G93A mSOD1 mice (Saxena et al., 2009). This study was followed up by another that showed that the ER cochaperone SIL1 was specifically expressed in ER stress-resistant motor neurons. The AMPA Receptor antagonist CNQX blocked motor neuron excitability and also decreased SIL1 expression. SIL1 null or heterozygous mice displayed an increased predilection for UPR signaling in response to neuronal lesions induced by crush injuries. Overexpression of SIL1 in G93A mice significantly increased lifespan and diminished disease symptoms, especially in G93A-s mice, which further demonstrated the protective role of SIL1 in motor neurons (de L'Etang et al., 2015). The inability of salubrinal to completely reverse the effects of the disease in G93A mSOD1 mice strongly suggests the presence of other mechanisms underlying ALS, including inflammatory processes. Sporadic ALS patients have been shown to possess pro-inflammatory cytokines MCP-1α and complement proteins in their cerebral spinal fluid and serum (Simpson et al., 2004; Goldknopf et al., 2006). In a study of 144 sALS patients, IL-18 was specifically found to be elevated in the CSF and sera compared to the control group (Italiani et al., 2014). Inflammatory cytokine IFNγ was shown to trigger CHOP expression in spinal cord neurons in sALS patients via induction of iNOS. TNFα exposure to astrocytes for 72 h in culture led to upregulation of glutamate receptors and enhanced the risk for glutamatergic toxicity (Dumont et al., 2014). When a TNFα antagonist was given to mSOD1 mice, there was a small but significant increase in lifespan (West et al., 2004). One study also showed that release of mSOD1 by neurons activated microglia and promoted cell death (Urushitani et al., 2006). Other studies also found that cyclooxygenase-2 was increased in spinal cords of ALS patients and that celecoxib delayed onset of the disease in mice, although it did not inhibit progression (Yasojima et al., 2001; Drachman et al., 2002; Yiangou et al., 2006). Areas that remain unanswered involve elucidating/reconciling the mechanism behind ER stress-induced apoptosis in motor neurons, the various other mutations behind fALS (including TDP-43, alsin, senataxin, VAPB, dynactin, and angiogenin), the triggers of ER stress in sALS, and the role of SIL1 in motor neurons. Salubrinal has been shown to alleviate symptoms and slow progression of the disease in mouse models but does not completely cure ALS in the mSOD1 mouse model, suggesting multiple mechanisms besides ER stress behind selective motor neuron loss.

Parkinson's disease is a neurodegenerative disease in which the number of dopamine-releasing neurons of the substantia nigra pars compacta is compromised. The cause of the neuronal loss is largely unknown, although it has been postulated that ER stress and inflammatory mechanisms may contribute to neuronal death. Three proteins have been associated with the pathogenesis of PD: parkin, α-synuclein, and C-terminal esterase L1 (UCH-L1). Despite the role of α-synuclein being relatively unknown, it forms aggregates called Lewy bodies that are characteristic of PD and late-stage neurodegenerative diseases. Cooper et al. (2006) discovered that α-synuclein blocked ER-Golgi vesicular trafficking, which was rescued by Rab1, a guanosine triphosphatase. The expression of parkin, a ubiquitin E3 ligase, is induced by ER stress, and its activity was shown to protect against ER

stress-mediated apoptosis in neurons (Imai et al., 2000). UCH-L1 has been linked to ERAD through ubiquitination of unfolded proteins (Liu et al., 2002). In addition, the expression of ER foldase PDI is induced in neurons of PD patients, and PDI is also found in Lewy bodies in patients with PD (Conn et al., 2004).

PD has also a well-recognized inflammatory component. Release of α-synuclein extracellularly may activate microglial cells and lead to an inflammatory reaction (Zhang et al., 2005; Reynolds et al., 2008). CD4+ T regulatory cells were also found to mediate microglial activation by nitrated α-synuclein (Benner et al., 2008). In addition, exposure of LPS was sufficient to induce dopaminergic neuron loss, presumably through microglial TLR4 since neither astrocytes nor neurons expressed TLR4 at significant levels (Castano et al., 1998; Kim et al., 2000). LPS exposure also led to upregulation of COX-2 and iNOS (Hunter et al., 2007). Reactive oxygen species, IL-1β, TNF-α, and NO have also been implicated in the inflammatory response mediated by microglial activation (Hirsch et al., 2012). The importance of the ER stress and ERAD in familial forms of Parkinson's disease implies additional downstream mechanisms such as oxidative stress, mitochondrial dysfunction, and inflammatory mechanisms may be involved in the same pathway. Further studies should identify how UPR pathways, including IRE1 and XBP1, affect neuroinflammation in the pathogenesis of PD.

Discussion

ER stress and inflammation are linked through numerous mechanisms and in various disease states, including autoimmunity and infection, metabolic disorders, and neurodegenerative diseases. However, it is often unclear which of these two pathways contains the initiating signal. For instance, in obesity, ER stress triggers the inflammatory pathway to generate pro-inflammatory adipocytes, which later may exacerbate ER stress. Meanwhile, IFNγ, through induction of iNOS, initiates CHOP expression and downstream pro-apoptotic signaling in spinal cords neurons of sporadic ALS patients. In Parkinson's disease, ER stress and inflammation appear to work in parallel, potentially with a common upstream signal (e.g., α-synuclein). It appears as though how and when ER stress and inflammation operate in concert remains highly dependent on the context of specific diseases and signaling molecules, especially since numerous molecules are still being found to have novel functions in the ER stress and inflammatory pathways.

Secretory cells are canonically prone to ER stress, due to the massive production of secretory proteins. Moreover, release of misfolded protein may promote an inflammatory response in secretory cells. Many diseases, including IBD, Parkinson's disease, diabetes, rheumatoid arthritis, and states of viral infection, are perpetuated by the release of antigenic factors that play a dual role in inducing the UPR and inflammation. On the other hand, non-secretory cells have been shown in myriads of cases to be involved in both pathways. Under inflammatory conditions, ER homeostasis may be easily disrupted even without a high protein folding load. More and more evidence suggest that ER dysfunction is a universal phenomenon in inflamed cells regardless of the cells' secretory status. Therapeutics for diseases that have been clinically established as inflammatory in origin often focus on anti-inflammatory treatments, which show various efficacy and significant side effects. Treatments targeting both ER stress and inflammation simultaneously may open a new avenue for diseases with pathogenic contributions from both pathways.

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