Mechanisms of disordered neurodegenerative function: Concepts and facts about the different roles of the protein kinase RNA-like endoplasmic reticulum kinase (PERK)

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Mechanisms of disordered neurodegenerative function: concepts and facts about the different roles of the protein kinase RNA-like endoplasmic reticulum kinase (PERK)

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Abstract: Neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, prion disease, and amyotrophic lateral sclerosis, are a dissimilar group of disorders that share a hallmark feature of accumulation of abnormal intraneuronal or extraneuronal misfolded/unfolded protein and are classified as protein misfolding disorders. Cellular and endoplasmic reticulum (ER) stress activates multiple signaling cascades of the unfolded protein response (UPR). Consequently, translational and transcriptional alterations in target gene expression occur in response directed toward restoring the ER capacity of proteostasis and reestablishing the cellular homeostasis. Evidences from *in vitro* and *in vivo* disease models indicate that disruption of ER homeostasis causes abnormal protein aggregation that leads to synaptic and neuronal dysfunction. However, the exact mechanism by which it contributes to disease progression and pathophysiological changes remains vague. Downstream signaling pathways of UPR are fully integrated, yet with diverse unexpected outcomes in different disease models. Three well-identified ER stress sensors have been implicated in UPR, namely, inositol requiring enzyme 1, protein kinase RNA-activated-like ER kinase (PERK), and activating transcription factor 6. Although it cannot be denied that each of the involved stress sensor initiates a distinct downstream signaling pathway, it becomes increasingly clear that shared pathways are crucial in determining whether or not the UPR will guide the cells toward adaptive prosurvival or proapoptotic responses. We review a body of work on the mechanism of neurodegenerative diseases based on oxidative stress and cell death pathways with emphasis on the role of PERK.

Keywords: apoptosis; autophagy; endoplasmic reticulum stress; mitochondrial stress; unfolded protein response.

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Introduction: the endoplasmic reticulum

The endoplasmic reticulum (ER) is made up of an intercommunicating membranous network that spreads throughout the cell cytoplasm from the nuclear envelope (NE) to the cell membrane and comprises an anastomosing narrow tubules, cisternae, and vesicles. The ER represents a major site for protein and lipid biosynthesis as well as fundamental cellular functions owing to its wide membrane surface, which is 30 times that of the cell membrane (Mescher, 2013).

The membranes of the flattened cisternae are contiguous with the outer membrane of the NE, the latter of which consists of double membrane sheets that meet only at the nuclear pores and hence can be described as nuclear ER. The tubular network is highly curved and extends

throughout the whole cytosol, the water-soluble component of the cytoplasm within which organelles are suspended. This highly branched tubular network is referred to as peripheral ER. The luminal spaces of the peripheral ER are in continuity with that of the nuclear part presenting >10% of the total cell volume. Moreover, the ER is in close contact with all other organelles in the cell, including the plasma membrane (PM), Golgi apparatus (G), vacuoles, mitochondria, peroxisomes, late endosomes, and lysosomes, where the contact sites represent separate ER domains (Voeltz et al., 2002; Okeke et al., 2016; Van Anken and Sitia, 2016).

ER cisternae collect the newly synthesized proteins for the process of maturation, folding, modification, and delivery to other organelles via secretory pathways. Over a quarter of all proteins are either transferred into the ER lumen or integrated into ER membranes. The cytosolic side of the ER membrane has polyribosomes, which are scattered at many sites and considered the point of discrimination between rough (RER) and smooth (SER) ER in which polyribosome is present on the former surface (Mescher, 2013).

The ER possesses various functions that include (1) synthesis; SER is the place of lipid biosynthesis, carbohydrate metabolism, and temporary calcium sequestration, while RER is the site for protein synthesis used for secretion, translocation across the ER membrane, integration into the PM, and as enzymes within lysosomes; (2) transport molecules across the cell, segregated away from the cytoplasm; (3) storage of the nascent molecules; and (4) detoxification where the SER detoxify drugs and alcohols. Further functions involve glycosylation of glycoproteins, posttranslational modification of the newly formed polypeptides, and assembly of multichain proteins. These vital activities are regulated by resident enzymes of RER and by protein complexes known as chaperones that guide the folding of the newly formed proteins, buffer the load, and generally assure quality control of proteins within the ER (Ma and Hendershot, 2001; McMaster, 2001; Hetz and Mollereau, 2014; Milisav et al., 2015).

The Golgi apparatus (G) has a dynamic relationship with the ER in which the molecules travel from RER cisternae via membrane-enclosed carriers called transporters to G. Such transport vesicles fuse with cis face that is the Golgi-receiving side, whereas the G trans face on the opposite side of G network shows larger saccules that produce other vesicles responsible for carrying completely formed proteins to organelles away from G (Mescher, 2013).

The production of the transport and secretory vesicles is forced by a group of coating proteins that meanwhile control the trafficking between G and ER. In the cis G network (CGN), vesicle movement from the RER and forward through the CGN is promoted by coat protein II (COP II), while COP I controls the retrograde movement of vesicles. The whole process of transport is enabled by a cytosolic network composed of cytoskeletal polymers and motor proteins, which are able to change its assembly/disassembly ratio in response to regional needs (Mescher, 2013). Both human and animal cells' cytoskeleton are composed mainly of microtubules (MTs) made up of polymerized tubulin, which are found to be disturbed in some neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD) (Milisav et al., 2015).

Mitochondria-associated ER membranes (MAMSs) are ER membranes adjacent to mitochondria that permit transport of membrane lipids, lipid, Ca^{2+}, and reactive oxygen species (ROS) to the mitochondria as well as participate in autophagosome formation and regulation of autophagy by mitochondrial membranes (Hamasaki et al., 2013; Marchi et al., 2014). MAMS offers a direct communication channel between the ER and mitochondria that allows transfer of Ca^{2+} stored in significant amounts from the ER lumen to mitochondria in order to maintain cellular metabolism and, hence, cell survival (Patergnani et al., 2011; Bononi et al., 2012; Raturi and Simmen, 2013).

Proteostasis and ER stress

Protein folding and maturation are important, even vital, processes that require intact ER, the main subcellular organelle involved in such a process and where around one-third of the total proteome is produced. Therefore, balanced protein homeostasis known as proteostasis necessitates a well-organized process of folding of the recently formed proteins and degradation mechanisms that get rid of the unfolded/misfolded proteins and hence prevent aggregation of abnormal proteins (Shen et al., 2004; Hetz et al., 2013; Hetz and Mollereau, 2014).

The protein-folding system consists basically of cytoplasmic and ER-resident chaperones that regulate folding of the biologically active native proteins within the cellular environment where the correctly folded proteins will be transported to G apparatus, which is responsible for protein maturation and distribution to membrane environment such as PM. Concurrently, the quality control mechanisms identify the unfolded/misfolded proteins and facilitate their degradation through the ER-associated degradation (ERAD), cytosolic proteasomes, and lysosome-mediated autophagy (Yoshida, 2007; Pereira, 2013; Hetz and Mollereau, 2014; Liu et al., 2015).

Consequently, the capacity of the ER to control the protein-folding system is overwhelmed by any number of contributors to different means of ER stress (ERS); in certain pathological conditions, such as extracellular blood glucose concentration fluctuation, oxidative stress, toxic agents/drugs, and radioactive radiation, the abnormal unfolded/misfolded proteins will be accumulated in the lumen of the ER (Schröder and Kaufman, 2005; Yoshida, 2007; Liu et al., 2015).

The more the overproduction of the unfolded/misfolded proteins, the more they accumulate in ER, with a disturbed quality control system. Ultimately, the unfolded protein response (UPR) will be activated to restore proteostasis by a series of adaptive mechanisms that affect many aspects of the secretory pathway. Conversely, if cell damage is sufficiently severe, UPR signaling results in cell death by apoptosis (Schröder and Kaufman, 2005; Yoshida, 2007; Hetz et al., 2013).

The UPR initiates three main adaptive mechanisms to relieve stress and restore homeostasis. The first is to induce general translational arrest to reduce and even stop the influx of newly formed proteins into the ER. The second is to stimulate transcriptional up-regulation of the genes that enhance the ER protein folding capacity and quality control. The third is to induce the degradation mechanisms of the proteins with aberrant conformation through ERAD, cytosolic proteasome, and lysosome-mediated autophagy (Pereira, 2013).

UPR, stress sensors, and downstream signaling pathway

The UPR involves two chief elements. The first is a set of key stress trans-membrane protein sensors located on the ER. The second is downstream transcription factors that remarkably regulate gene expression, resulting in a cellular response that ranges from adaptation to stress, resulting in cell survival. In addition, autophagy or induction of apoptosis that ends in cell death is wholly dependent on the severity of the stress-induced injury. Gene expression regulation occurs at one of the three stages of gene production that includes transcription, translation, and degradation (Raven et al., 2008).

Principally, there are three key players in the UPR pathway and considered as stress sensors: protein kinase RNA-activated-like ER kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and the activating transcription factor 6 (ATF6) (Ron and Walter, 2007). Under normal physiological conditions, the activities of the three trans-membrane sensor molecules are blocked by the ER chaperone known as glucose-regulated protein 78 (GRP78), which binds to the ER lumen. GRP78, a member of heat-shock protein 70 (Hsp70) family, is a highly expressed ER-resident protein that guards against misfolding/unfolding of the proteins through an active process via its N-terminal ATPase domain. It binds to the hydrophobic domain of the proteins with its C-terminal substrate-binding domain (Szegezdi et al., 2006; Liu et al., 2013, 2015; Hetz and Mollereau, 2014).

However, when the ERS continues to be excessive, the ER chaperone GRP78 dissociates from those stress-sensing proteins to promote their activation via two different mechanisms; one involves IRE1α and PERK and occurs by induction of self-phosphorylation and oligomerization, whereas the other mechanism involves translocation of ATF6 to the Golgi, where it is activated after being cleaved by site 1 and site 2 proteases (S1P and S2P) (Szegezdi et al., 2006; Ron and Walter, 2007; Liu et al., 2013; Pereira, 2013).

ATF6 is a type II protein sensor located in the ER membrane of the unstressed cell and contains Basic Leucine Zipper Domain (bZIP) transcription factor in its cytosolic domain (C-terminal). ATF6 is inactive by binding to GRP78 during the resting state. During extended ERS, ATF6 will be dissociated from GRP78 and undergoes a process of activation that is initiated by its translocation to Golgi apparatus, where it is cleaved by S1P and S2P to release its bioactive cytosolic fragments: ATF6f. ATF6f is also known as ATF6 P50 and is considered the bioactive form of the ATF6 because it implies the bZIP nuclear transcription activation domain that is generated from the N-terminal region of the ATF6. Accordingly, ATF6f translocates to the nucleus to activate the transcription and, eventually, the expression of ERAD genes and X-box binding protein 1 (XBP1) (Ye et al., 2000; Hetz et al., 2013, Hetz and Mollereau, 2014; Liu et al., 2015). ATF6f performs its function either solely or through combination with activated spliced XBP1s to form heterodimers to control the induction of specific patterns of gene expression (Shoulders et al., 2013).

IRE1α possesses double enzymatic function owing to its endoribonuclease and Ser/Thr kinase domains. The activated IRE1α will initiate up-regulation of the genes that mediate ERAD, protein quality control, and biogenesis. Once the IRE1α is activated by autophosphorylation, dimerization, and oligomerization, the RNase domain will be activated accordingly, which will trigger excision of 26-nucleotide introns of the messenger RNA (mRNA) encoding the transcription factor X-box-binding protein 1 (XBP1) in an unusual way, resulting in shifting of the coding reading frame of the mRNA. This splicing process will ultimately lead to the expression of the spliced variant

of the XBP1 which is an active form known as XBP1s. XBP1s will then up-regulate target genes involved in UPR; protein folding process, maturation, and transportation to the ER; and degradation, secretions, and lipid synthesis as well (Hetz et al., 2013; Pereira, 2013; Liu et al., 2015). IRE1α mediates UPRosome that implies various adaptors and regulators (Hetz and Glimcher, 2009; Hetz, 2012). The crystal structures of ATF4, IRE1α, and ATF6 proteins are mentioned in Figure 1.

Additionally, IRE1α is considered a trigger of stress-induced cell death, which, together with tumor necrosis factor (TNF) and TNF-receptor-associated factor 2 (TRAF2), initiates the downstream activation of the alarm kinases, apoptosis signal-regulating kinase 1 (ASK1) and JUN N-terminal kinase (JNK) (Urano et al., 2000; Nishitoh et al., 2002). IRE1α RNase activity, moreover, degrades a group of protein-folding-related mRNAs that specifically encode proteins and their secretory pathway through a process described as regulated inositol-requiring enzyme 1 (IRE1)-dependent decay (RIDD) of mRNA. This degradation process depends on the cell type, the tendency of the encoded protein to misfold, and similarly on the presence of a conserved nucleotide sequence along with a well-defined secondary structure. Several studies suggest that cell death is stimulated by the RIDD process. In addition, IRE1α likewise can cleave premature microRNAs (MiRNAs), which affect the regulation of apoptosis. MiRNAs have been shown to influence the biological functions of IRE1α via regulation of its expression levels (Hollien and Weissman, 2006; Han et al., 2009; Hollien et al., 2009). There seems to be an agreement that IRE1α signaling pathway is the most conserved branch of UPR and the only one recognized in yeast (Hetz et al., 2013; Hetz and Mollereau, 2014; Liu et al., 2015).

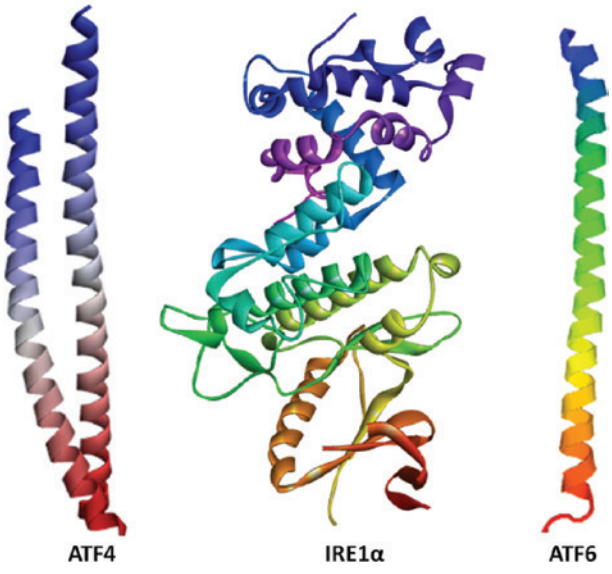

Figure 1: Structural depiction of ATF4, IRE1α, and ATF6 proteins.

PERK is activated as one of the major signaling pathways of the ERS and UPR that controls a rapid temporary translation inhibition, which leads to reduction of misfolded proteins load in the ER by decreasing general protein synthesis and therefore reducing their entrance into the ER lumen (Hetz and Mollereau, 2014). The process of PERK activation involves autophosphorylation and dimerization with ensuing formation of large clusters; the process similar to IRE1α activation (Hetz et al., 2013). Activated PERK, a member of eIF2α kinase family, phosphorylates the α-subunit of α-subunit of eukaryotic initiation factor 2 (eIF2α). The phosphorylation of eIF2α is carried out by a family of four protein kinases, PERK, protein kinase double-stranded RNA dependent, general control nonderepressible-2, and heme-regulated inhibitor (Hamanaka et al., 2005; Raven and Koromilas, 2008; Donnelly et al., 2013).

Upon cellular stress that occurs due to a wide range of internal stresses and environmental exposures such as heme deficiency, oxidative stress, amino acid starvation, toxic agent/drug, radioactive radiation, and viral infection, these kinases will be activated, which then initiates the phosphorylation of eIF2α, a protein which is significantly involved in translational control, on a specific serine residue (Ser51) located within the alpha subunit leading to a global translation attenuation, and thus, protein synthesis is arrested. However, while a similar downstream sequence exists among the four eIF2α kinases in their kinase domains, resulting in common pathway phosphorylating eIF2α, further differentiation criteria would determine which specific signals will activate them (Donnelly et al., 2013; Liu et al., 2015; Milisav et al., 2015).

In response to ERS, PERK will be dissociated from GRP78 and then will be activated by dimerization and auto phosphorylation. eIF2α, which is one of the PERK's downstream effectors, will, as a result, be activated by phosphorylation at the alpha subunit, resulting in inhibition of new protein synthesis via inhibition of gene expression at the step of translation. The suppression of the transportation of initiator methionyle-tRNA to the ribosome leads to global protein cap-dependent translation. This remarkably represents a prosurvival signaling pathway that reduces the proteins entering the ER lumen, which ultimately buffers the misfolded protein load and is hence considered a cell survival factor (Raven et al., 2008; Raven and Koromilas, 2008; Donnelly et al., 2013; Hetz et al., 2013; Liu et al., 2015).

Simultaneously, eIF2α activation will conversely enhance selective translation of mRNAs with the internal

entry ribosomal site, namely, ATF4, a member of the bZIP family of transcription factors that regulates the expression of several target UPR genes encoding proteins involved in antioxidant responses, amino acid metabolism, energy production, and protein folding together with ER chaperones and foldases (Pereira, 2013; Milisav et al., 2015). As a downstream effect of PERK and ATF4, the transcription factors nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and nuclear factor-κB (NF-κB) are phosphorylated, resulting in further regulation of redox metabolism and inflammatory processes (Milisav et al., 2015).

During sustained ERS, PERK and ATF4 play a role in proapoptotic signaling and control the expression of several genes involved in autophagy and apoptosis, such as C/EBP-homologous protein (CHOP). The transcription factor regulating proapoptotic B-cell lymphoma (BCL2) genes and DNA damage-inducible 34 (GADD34) participate in a feedback circle to restore cap-dependent translation and, hence, protein synthesis via dephosphorylation of eIF2α through interacting with protein phosphatase 1C (PP1C). Such downstream pathways are considered important, even vital, when ERS is prolonged or eventually cannot be alleviated and may contribute to neurodegeneration (Averous et al., 2004; Hetz et al., 2013; Pereira, 2013; Milisav et al., 2015).

The translational control triggered by the PERK/eIF2αP/ATF4 cascade is not the only identified PERK mechanism in UPR, but it was found that ATF6 and its target genes were activated by the same pathway with resultant activation of the transcriptional phase of UPR. The PERK pathway enables synthesis and trafficking of ATF6, in which primarily ATF4 up-regulates the transcription of the gene encoding ATF6, resulting in the production of satisfactory amounts of newly formed ATF6 available to ensure continuous processing into activated ATF6. Second, ATF4 contributes to the transport of ATF6 from the ER to the G for next proteolysis and splicing activation by S1P and S2P. Mutations that influence any of the steps of the PERK/eIF2αP/ATF4 pathway will considerably reduce the levels of activated ATF6 in response to either tunicamycin or thapsigargin treatments (Teske et al., 2011). In accordance, loss of PERK decreases the translational and transcriptional phases of the UPR through significantly reduced ATF6 activation, leading to diminished protein chaperone expression, interruption of lipid metabolism, and facilitation of cell death and apoptosis (Wu et al., 2007; Yamamoto et al., 2007; Rutkowski et al., 2008; Yamamoto et al., 2010). These findings strongly support the idea of introducing the UPR signaling transduction as a highly integrated regulatory network and help in considering PERK with its diverse biological influence as a crucial therapeutic target.

PERK-associated pathway in ERS-induced autophagy

Lysosomes represent intracellular spots responsible for digestion and cellular turnover. They are membrane-limited vesicles that encompass nearly 40 hydrolytic enzymes and are shown to be functional in degradation of the exogenous macromolecules and removal of damaged organelles. The cytoplasmic structure is another function possessed by lysosomes and called autophagy. The damaged organelle or cytoplasmic portion becomes surrounded by an isolation membrane composed of autophagy-related (Atg) proteins from SER forming autophagosome with the assistance of ubiquitin-like protein conjugation systems, namely, the light chain 3 (LC3) and Atg12 protein systems, which modify autophagic proteins such as Atg8 and Atg5. Consequently, the autophagosomes are bound to lysosomes that digest the enclosed cytoplasm. The digested products from the autophagosome are reused by the cytoplasm. At the subcellular level, ER served as a platform for induction of autophagy (Mijaljica et al., 2006; Ouyang et al., 2012; Mescher, 2013).

ERS signaling could act as a trigger shifting the cellular response from autophagy to apoptosis. Upon ER stress, activation of signal transductions ensue with the autophagic gene are found as targets of ER stress-related transcriptional factors (B'chir et al., 2013; Margariti et al., 2013; Gade et al., 2014; Moon et al., 2015). One of the main mechanisms of Huntington's disease (HD) is the accumulated mutant Huntington (Htt) aggregation that induces neuronal cytotoxicity, which could be degraded by autophagy pathway as cell protective mechanism. However, such a pathway was found to be disturbed by IRE1/TRAF2 ERS signaling. Upon phosphorylation and dissociation of Beclin1 from BCL2, death-associated protein kinase 1 (DAPK1) initiates autophagy. ATF6 is considered a positive regulator for autophagy by interacting with ERK1/2 target site of C/EBP-β leading to production of heterodimer that activates the promoter of DAPK1 (Hoozemans et al., 2005; Kieran et al., 2007; Zuleta et al., 2012). PERK is essentially involved in induction and regulation of ERS-induced autophagy via two main pathways.

eIF2α/ATF4 pathway

In the autophagic induction phase, PERK activation will lead to phosphorylation of eIF2α and, consequently, activation of many eIF2α phosphorylation-dependent selective translation that leads to Atg12 up regulation. The

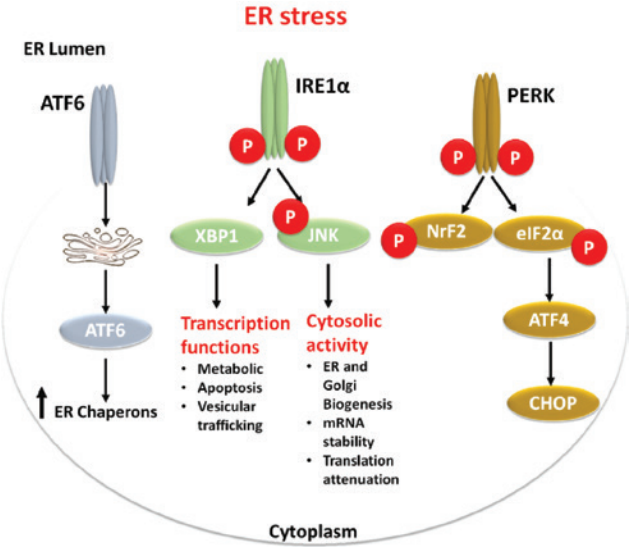

Figure 2: ERS-mediated signaling pathways through the activation of ATF6, IRE1α, and PERK.
The activated ATF6 protein mediates chaperons and downstream signaling pathway through G apparatus. The activated IRE1α upon phosphorylation activates two proteins such as XBP1 and JNK, respectively. Moreover, phosphorylated JNK is directly involved in cytosolic activities such as ER and G biogenesis mRNA stability and translational attenuation, whereas XBP1 controls some transcription functions like metabolic activity, apoptosis, and vesicular trafficking. The PERK protein regulates couple of downstream signaling proteins such as Nrf2 and eIF2α. eIF2α mediates ATF4, which controls CHOP functionality.

later will stimulate Atg5-Atg12-Atg16 complex formation, causing promotion of LC3-I to LC3-II conversion (Kouroku et al., 2007; B'chir et al., 2013). It was found that ATF4 activation is crucial in the regulation of several autophagic gene transcriptions, such as Atg3, Atg12, Atg16, mitogen activated protein (Map), Becn1, and Gabarapl2, which were identified as target genes for ATF4 by a previous study using chromatin immunoprecipitation analysis. In addition, ATF4 and CHOP activation enhances transcriptions of autophagic genes including Atg7, Nbr1, and Sqstm1 (B'chir et al., 2013; see Figure 2).

AMP-activated protein kinase/mammalian target of rapamycin 1 pathway

In endothelial cells during extracellular matrix (ECM) detachment, autophagy is found to be regulated by PERK through modulation of the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin 1 (mTORC1) pathway, the latter of which is a protein kinase controlling multiple cellular metabolic functions (Zarogoulidis et al., 2014). mTOR is a negative autophagic regulator that, when suppressed, causes autophagy stimulation by regulating Atg1 in yeast and Atg1 complex, ULK (UNC-51-like kinase), in mammals. The disturbance in adenosine triphoshate (ATP)/ adenosine diphaosphate ratio would lead to the activation of AMPK, which then inhibits the mTOR activity, resulting in autophagy (Shi et al., 2012). PERK essentially activates AMPK phosphorylation at the AMPK site, which is a substrate for the tumor suppressor serine-threonine kinase (LKB1), also referred to as STK11, that is responsible for Peutz-Jeghers Syndrome (Avivar-Valderas et al., 2013). To our knowledge, the PERK/AMPK/mTORC1 pathway, which induces autophagy, was identified only in endothelial cells. Therefore, more studies are yet needed to describe such mechanism and whether or not to be considered a common pathway.

Role of PERK pathway in shifting signal transduction from ER-induced autophagy to apoptosis

It is believed that the contribution of PERK/eIF2α/ATF4 pathway in ERS-mediated apoptosis and autophagy is somehow, confusing issue due to the well-known protective role of autophagy in contrary to that of apoptosis. Nevertheless, some studies in selenite-treated leukemia NB4 cells showed that PERK/eIF2α/ATF4 pathway per se regulated the shift from autophagy to apoptosis through factor p38 that control the switch in signaling and which PERK regulates its phosphorylation (Jiang et al., 2014).

In a study on selenite-induced cell death and autophagy suppression *in vitro* and *in vivo*, it was found that cell death was promoted by autophosphorylation at Thr^{180}/Tyr^{182} with the activation of p38, which was consistent with the results of Keil et al. (2013). However, an opposite relation between p38 and autophagy has been illustrated by several other studies, suggesting that p38 has a dual role as promoter or inhibitor of autophagy depending on stimulus type (Corcelle et al., 2007; Zheng et al., 2012).

Besides the classical MKK3/6 (MAPK kinase) pathway promoting p38 activation in circumstances of ERS, Hsp90 contribute as p38 activator as well. Hsp90 is typically described as a molecular chaperone regulating the maturation of ER sensing proteins, IRE1α and PERK, the latter of which affects Hsp90 expression (Park et al., 2008; Manni et al., 2012; Zheng et al., 2012).

Selenite-induced PERK activation was shown to decrease Hsp90 expression and afterward led to p38

autophosphorylation. It was revealed by the same study that p38 impacts the expression of both CHOP-related apoptosis pathway and autophagy-associated MT-associated protein 1 light chain 3B (MAP1LC3B) genes. In selenite-treated cells, p38 activation will stimulate eIF2α and eIF2α downstream with resultant promotion of different gene expression. Nevertheless, after selenite treatment, ATF4 tended to bind the CHOP promoter rather than MAP1LC3B promoter because of a p38-mediated up-regulation of eIF2α ~ P and down-regulation of p-eIF4E. This characteristic influence demonstrated by p38 in regulation of eIF2α and eIF4E is thought to determine the transcription of the key protein players and, consequently, the switch from autophagy to apoptosis (Jiang et al., 2014).

In cancer studies, there has been a considerable discussion on the inconsistent role of autophagy and UPR signaling that remarkably depends on the cancer type and the kind of stimulus and in which initiation of autophagy has been found to induce apoptotic signals resulting in programmed cell death (Levine, 2007). It has been believed also that the level of ERS would determine UPR signaling (Schönthal, 2009). Although metformin-induced autophagy is considered a prosurvival factor and has been demonstrated as a protective mechanism in esophageal squamous cell carcinoma, it was found to cause death in lymphoma cells and melanoma (Tomic et al., 2011; Feng et al., 2014). Similarly, UPR in response to ERS mediates cell survival of leukemic cells as well as facilitates apoptosis in lung and gastric cancer (Ni et al., 2009; Wu et al., 2010; Xin et al., 2013). Autophagy and PERK signaling are shown to be important pathways in protection of ovarian cancer cells against metformin stress, in which their inhibition causes growth suppression and induces cancer cell apoptosis (Moon et al., 2015).

The recorded role of autophagy and PERK as a protective factor for cancer cell may potentially contribute to the resistance of cancer cells to chemotherapy (Ranganathan et al., 2006; Chen et al., 2010). Therefore, autophagy and PERK represent essential therapeutic targets in order to sensitize cancer cells to chemotherapy (Chen et al., 2010; Yang et al., 2011; Suh et al., 2012). It was confirmed that combining metformin as an ovarian cancer treatment with autophagy inhibitors neither showed an impact on the normal peripheral blood mononuclear cell (PBMC) and ovarian surface epithelial cell growth nor resulted in their apoptosis. Furthermore, treatment with metformin and PERK inhibitor was found to enhance apoptosis in ovarian cancer cells but not in PBMCs. Those findings confirm that pharmacologic inhibition of autophagy and PERK potentiated the cytotoxicity of metformin, with no apparent effect on normal cells. It is known that metformin is an anticancer agent; however, its treatment outcome was recommended to be improved by its combination with autophagy and/or PERK inhibitors in order to control ovarian cancer (Moon et al., 2015).

Cell survival and programmed cell death (apoptosis)

During cell resting conditions, the ER chaperones bind to the ER luminal domains of UPR stress sensors. Upon ERS, such bonds are dissociated, resulting in signal activation aiming at initiating adaptive responses that ensure cell survival. Although CHOP is introduced widely as the major protein involved in the ERS-induced apoptosis, it is considered a part of caspase-dependent cell death cascade. CHOP is activated by ATF6 as well (Liu et al., 2015). GADD34 induces cell death and also resumes protein synthesis in stressed cells (Hetz et al., 2013). However, GADD34, death receptor 5, ER oxidase 1, and other apoptotic molecules are believed to be target molecules that receive apoptosis signals from CHOP transcription protein. Caspase cascade activation is believed to be involved in ERS-induced apoptosis, including caspase-2, caspase-4 (human), caspase-12 (rodents), caspase-3, caspase-7, and caspase-9, in which caspase-12 and caspase-4 were inclined in ERS death signals rather than other cell death mechanisms (Liu et al., 2015).

Further mechanisms that determine the cell fate occur via IRE1α signaling, which leads to activation of mitogen protein kinase, described as c-JNK and the transcription factor XBP-1 to promote its active spliced form XBP-1s (Chen and Brandizzi, 2013; Hetz et al., 2013; Milisav et al., 2015). XBP-1 regulates target gene expression encoding proteins associated with a wide range of ER functions: protein folding process, maturation, transportation to the ER, degradation, secretions, and lipid synthesis, as well as ER chaperone and glycosylation enzymes (Hetz et al., 2013; Pereira, 2013; Dufey et al., 2014; Liu et al., 2015).

Other mechanisms have been demonstrated as other contributors in the apoptotic pathways and cell death. The MAM, which represents the communication channel between ER and mitochondria, allows Ca^{2+} coupling and flux of its stored form to the ER lumen. Interruption of the contact sites due to exposure to ERSs will lead to impairment of Ca^{2+} coupling between the ER and mitochondria, which will deleteriously impact the cellular function, and in severe stresses, apoptosis may occur. Therefore, the balance in the amount of calcium transferred from the ER to the mitochondria is extremely essential (Logue et al., 2013).

The distance between the two compartments is another factor that determines the integrity of the membranes and the amount of Ca^{2+} flux from the ER to the mitochondrial matrix. Increasing the distance will decrease Ca^{2+} mobility to the mitochondria, resulting in disturbance in the Ca^{2+}-dependent-mitochondrial metabolism and ATP production, ultimately leading to cell death. On contrary, the narrow distance will enhance mitochondrial Ca^{2+} load, leading to defective permeability of the outer mitochondrial membrane that induces the release of proapoptotic factors like cytochrome c, finally leading to apoptosis through apoptosome formation and caspase activation (Bravo et al., 2012).

The MAMs are molecularly controlled by ER inositol 1, 4, 5-triphosphate receptor (IP_3Rs), and voltage-dependent anion channels present on the outer membrane of the mitochondria. Both are coupled via glucose regulated protein 75kDa (GRP75), a cytosolic chaperone. The calcium transport into mitochondrial matrix occurs through the mitochondrial calcium uniporter (MCU), which is activated by microdomains of high calcium concentration formed by IP_3Rs together with ryanodine receptors (RyR) (De Brito and Scorrano, 2010).

The close contact between the two organelles is controlled by dynamin-related GTPase mitofusin2 (Mfn2) located on the ER, whichs form homo-heterodimers with Mfn1 or Mfn2 that presents on the mitochondrial matrix. Additionally, phosphofurin acidic cluster sorting (PACs-2) (located mainly at the ER), together with dynamin-related GTPase protein 1 (Drp1), regulates the distance between the two organelles via controlling the mitochondrial morphology and distribution (Cardenas et al., 2010). The MAM is associated with any transfer disturbance. This is evidenced by a small interference RNA knockdown of PACS-2, which causes the suppression of Ca^{2+} release, leading to apoptosis (Simmen et al., 2005).

On balance, the level of ERS will accordingly determine the type of the cellular response. Three levels of response will ensue here and depend on the load on misfolded/unfolded proteins in the ER lumen and the degree together with duration of exposure to stress: the mild stress that initiates UPR as a feedback mechanism that reinforces protein folding, quality control, and degradation process. This will result in cell recovery and adaptation. If the ERS becomes more severe or sustained, the adaptive mechanisms will fail to resume proteostasis; hence, the accumulated abnormal proteins will be translocated to cytosol, where they undergo eradication by proteasome-mediated degradation and ERAD. Furthermore, UPR signaling will activate macroautophagy, an enhanced elimination mechanism, to get rid of the large protein aggregates and damaged organelles via the lysosomal autophagy pathway. Ultimately, if the stress cannot be relieved, apoptosis will occur (Pereira, 2013; Hetz and Mollereau, 2014).

However, there have been considerable discussion and debates on what mechanisms would determine which particular response will be the one initiated and whether this depends on the level of stress or would extend to involve the type of sensors activated. There are many factors that underlie the change in UPR pathway from prosurvival to proapoptotic response. However, the understanding of differential activation of UPR sensors in mammals is as yet limited. In yeast, IRE1 has been demonstrated as the only conserved UPR signaling pathway, while evidences from *in vitro* studies in mammalian cells showed that IRE1α activation may not be initiated. On the other hand, IRE1β is shown to bind misfolded proteins, in the same way of IRE1 activation in yeast according to several reports (Credle et al., 2005; Gardner and Walter, 2011; Kimata and Kohno, 2011; Oikawa et al., 2012; Hetz et al., 2013).

It is yet unclear what triggers differential activation and attenuation of stress sensor protein. For example, the IRE1α-XBP1 pathway is found ceased in cells undergoing chronic sustained ERS, whereas PERK signaling is found to be the only active one. Hence, the protective effects of XBP1 expression will be lost, and the expression of apoptosis targets of ATF4 and CHOP will be enhanced. A growing body of evidence supports that UPR response has a salient difference in signal transduction and that information is limited to enable full understanding about the intensity and the duration of the stress stimuli to promote cell adaptation or cell death (Hetz et al., 2013). In this review, focus on the role of PERK in neurodegenerative diseases.

Hormesis

The use of the idea of 'hormesis' has emerged strongly in clinical trials as a therapeutic approach to mitigate neurodegeneration. This has been achieved through the induction of a preconditioning state by exposing the cell to mild, nonlethal stress to promote adaptive responses and hence protect the cell from an upcoming stronger injury. The obvious application in medicine can be illustrated in induction of quick cycles of ischemic preconditioning that prepares the heart before cardiac surgeries. This whole process of mild ERS that induces a hormetic response is known as ER-hormesis (Matus et al., 2012; Mollereau, 2013).

ER-hormesis can be achieved by various stimuli that result in mild accumulation of misfolded proteins in the

ER. Nontoxic doses of an *N*-glycosylation inhibitor, tunicamycin, were used as a pretreatment in toxin-based models of PD and resulted in protection against degeneration involving up-regulation of autophagy and the selective activation of IRE1-XBP1 but not ATF4-CHOP pathways. Likewise, selective ablation of Xbp1 in the nervous system reduces the pathology related to mutant superoxide dismutase 1 (SOD1) or mutant Htt through autophagy up-regulation. Such adaptive ER-hormetic mechanisms may offer neuroprotection as recorded by several studies (Matus et al., 2009; Fouillet et al., 2012).

PERK and diseases

The great body of evidence from animal models highlights the canonical role of UPR in various disorders, including neurodegenerative disorders, cancer, metabolic diseases, brain and heart ischemia, diabetes, diabetic cardiomyopathy, inflammation, and liver dysfunction. Therefore, UPR has become a major target in the context of drug discovery. Initially, there was emphasis on the connection between ERS and diseases described as protein-misfolding disorders because genetic changes might be expected to lead to the expression of mutant proteins that aggregate in the ER, but later studies conducted on genetically modified animals in which key UPR elements were knocked out have demonstrated that UPR is closely related to physiological pathways and diseases (Schröder and Kaufman, 2005).

It is widely believed that the brain is a rich area for research in the context of ERS and UPR and that proteostasis in the brain is a more vulnerable vital process to disturbances than in other organs (Kraskiewicz and FitzGerald, 2012). However, there is insufficient information on the normal physiological level of UPR activity in the central nervous system (CNS), which is, indeed, extremely essential when it comes to the determination of the potential side effects of gene therapy or other therapies targeting UPR (Hetz and Mollereau, 2014). The neuronal susceptibility is attributed to their continuous dependence on oxygen and glucose, in which even a short event of hypoxia and/or ischemia would lead to great deleterious consequences. Additionally, loss of neuronal regenerative ability after apoptosis or necrosis makes neurons more prone to age-related changes of proteostasis together with exposure to high turnover and high metabolic rate in the cells involved in synaptic transmission (Lipinski et al., 2010; Brown and Naidoo, 2012).

Diseases such as AD, PD, HD, and prion diseases (PrDs) are described as heterogeneous classes of neurodegenerative diseases that share a common feature of accumulating misfolded pathological proteins with consequent activation of UPR signaling pathways (Ma and Klann, 2014). The three central components of such UPR were explained earlier in this article: IRE1, ATF6, and PERK (Wek and Cavener, 2007).

PERK stimulation or PERK inhibition?

Particularly, PERK-dependent pathway has been strongly involved in shaping the ERS response through regulation of both individual and common cascades with the two other arms of UPR, making PERK a key player in ERS signaling pathway. The concept of an ERS contribution to neurodegenerative diseases has become an attractive target for researchers over the past few decades in which PERK again, as a crucial component, has been demonstrated as potential therapeutic target for these diseases. The initial PERK activation, with its substrate, eIF2α, which leads to a reduction in global protein synthesis, is typically a protective cell response in reaction to the accumulated misfolded proteins, the hallmark feature of neurodegenerative diseases. However, the sustained prolonged activation of PERK/eIF2α impairs cognitive function due to prolonged inhibition of essential new protein synthesis involved in neuronal plasticity and memory formation. PERK/ATF4 moreover mediates neuronal loss by regulating proapoptotic mechanisms. Unexpectedly, a wide range of studies using genetic and pharmacological alteration of PERK have led to controversial scenarios in which PERK can either alleviate or aggravate the neurodegenerative manifestation and even demonstrates contradictory effects on disease course and fate. This has led, with no doubt, that PERK influence on neurodegenerative disease progression depends on which specific signaling mechanism will be transduced, and hence, the dose and duration of PERK treatment should be fine-tuned to achieve the targeted outcomes (Richter and Klann, 2007; Alberini, 2008). The implications of this have led to a claim as to whether or not PERK activation during cellular stress is deleterious rather than protective? And, hence, PERK inhibition would be a promising strategy in treatment of cognitive deficits in neurodegenerative diseases.

GSK2606414 is a PERK inhibitor molecule that affects PERK autophosphorylation that was used in prion-infected mice. It showed successful treatment results regarding the behavioral defects and other brain pathologies according to a study conducted by Moreno et al.

(2013). GSK2606414 shows high selectivity to PERK rather than other kinases, and its blood-brain barrier permeation is perfect (Hirsch et al., 2014). Therefore, it is considered a valuable target in a study of its effectiveness in other neurodegenerative disease models such as PD, HD, and AD. In accordance to these results, it was concluded that genetic knockdown of PERK in the forebrain of AD model mice improves AD-associated manifestation involving synaptic plasticity and memory impairments (Ma et al., 2013).

Nevertheless, despite the potential role of PERK inhibitors, suggested to be effective therapy in different neurodegenerative disease models, it should not be taken for granted that excessive inhibition of PERK as a major signaling pathway in cellular stress response could disrupt normal protein regulation and, consequently, neuronal response to cellular stress causing synaptic dysfunction (Trinh et al., 2012). Therefore, it is extremely important to adjust the dose and duration of treatment with PERK inhibitor in order to achieve the desired effect with reservation of capability to restore protein synthesis in response cellular stress-response (Zhang et al., 2002). Additionally, it is crucial to establish biomarkers for early detection of neurodegenerative disease models before the clinical manifestation (Galasko and Golde, 2013).

Tau are MT-associated proteins that are present in the neurons and control the MT assembly and stabilization (Morris et al., 2011). When they become hyperphosphorylated under pathological conditions, tau dissociates from the MTs, and the MT lose their function and consequently aggregate into abnormal toxic filaments (Ballatore et al., 2007). Intracellular tau accumulation is a neuropathological hallmark in a wide range of neurodegenerative disorders, generally known as Tauopathies, including AD, PD, progressive supranuclear palsy (PSP), dementia affecting frontotemporal area, and PrD. However, the mechanisms behind tau accumulation and hyperphosphorylation are yet unclear when crosstalks between this pathway and neurodegeneration are considered (Pereira, 2013).

PSP, a sporadic type of tauopathy, which is depicted by aggregation of tau protein isoforms with four MT-binding repeats, is genetically associated with PERK (Bruch et al., 2017). This was shown in a genome-wide association study that identified eIF2αK3 common variants encoding PERK as a risk factor for PSP (Höglinger et al., 2011). Abnormal PERK signaling is as well associated with taupathies, but the exact relation is yet to be explored.

Three tauopathy models were used in a study conducted by Bruch and colleagues using cultured human neuronal cell line with overexpression of the 4-repeat wild-type tau, treated with the environmental neurotoxin annonacin, and P301S tau transgenic mice. It was found that treatment with CCT020312, a pharmacological PERK activator, lessened tau phosphorylation and tau isoforms, improving the cell viability *in vitro*. Additionally, the PERK activator decreased pathological findings associated with tau aggregates *in vivo* and hence ameliorated memory and locomotor function. In P301S tau mice, PERK overexpression prevented dendritic spine and motoneuron loss. eIF2α, the PERK substrate, was found to be down-regulated in PSP brains and tauopathy models that explored PERK-Nrf2 as an alternative pathway responsible for beneficial effects in the tauopathies. Ultimately, the authors concluded that PERK activation may be considered a promising novel strategy for tauopathies (Bruch et al., 2017).

A different scenario has been recognized in HD and amyotrophic lateral sclerosis (ALS), where the impact of ERS on ALS has been investigated in SOD1 mutant mice, representing 2% of total cases (Hetz and Mollereau, 2014). With a hallmark feature of motor abnormalities, HD is an autosomal dominant neurodegenerative disease in which dementia and psychiatric symptoms occur as early and mild onset of adult life. In HD, progressive accumulation of misfolded mutant Htt protein as intracellular oligomers and inclusions and which result from glutamine expansion of nearly more than 40 repeats gives rise to disease characteristic of neuronal loss in the striatum (Vidal et al., 2012).

In ALS mouse models presenting susceptible and resistant motor neurons, gene expression analysis showed that chronic ERS is the initial pathological finding selectively detected in vulnerable neurons during the presymptomatic stage of the disease (Saxena et al., 2009). In such ALS models, steering the PERK signaling arm exposed a dual role in the disease, in which the PERK/eIF2α activation path offered a protective effect through buffering the unfolded proteins load in the ER (Saxena et al., 2009; Wang et al., 2011). However, the PERK/ATF4 path mediates proapoptotic mechanisms with resultant cell death (Matus et al., 2013). In accordance with those findings, ablation of expression of proapoptotic proteins, such as p53, up-regulated the modulator of apoptosis (PUMA), BCL2-interacting mediator of cell death. In addition, ASK1 offers protection against experimental ALS (Hetz et al., 2007a; Kieran et al., 2007; Nishitoh et al., 2008). On the other hand, unexpected protection against ALS has been demonstrated when XBP1 was targeted in the nervous system, probably due to a shift in cellular response toward autophagy levels, which triggered degradation of mutant SOD1 aggregates (Hetz et al., 2009). Likewise, when XBP1 was knocked out in the HD transgenic mouse model, similar results were demonstrated in which mutant Htt levels were markedly decreased with improved neuronal viability and motor

functions, suggesting that neuroprotective effects might occur due to induction of autophagy. However, a generated Htt transgenic mice lacking the transcription factor ATF4 showed no effects on mutant Htt levels even when two further anti-Htt antibodies were used. This suggests that XBP1 effects on mutant Htt levels are specific for the IRE1α branch of the UPR (Vidal et al., 2012).

The exact contribution of ERS to PrD pathogenesis is somehow unclear due to a lack of influence of deficient Xbp1 or caspase 12 on disease pathophysiology and progression. However, several studies indicated that prion replication leads to prolonged eIF2α phosphorylation with resultant inhibition of protein synthesis and translational capacity, which is responsible for the neurological and behavioral disturbance in experimental PrD (Steele et al., 2007; Hetz et al., 2008; Moreno et al., 2013) and in which administration of a PERK inhibitor would offer an animal protection against PrD-related neurodegeneration (Moreno et al., 2013).

Jellinger reviews the matter of neurodegeneration, which is defined by progressive dysfunction of specific populations of neurons, determining clinical presentation (Jellinger, 2009, 2010; Nagley et al., 2010; Fan et al., 2017). He poses the idea that interrelated mechanisms lead to programmed cell death as follows: abnormal protein dynamics due to deficiency of the ubiquitin-proteosome-autophagy system, oxidative stress and free radical formation, mitochondrial dysfunction, impaired bioenergetics, dysfunction of neutrophils, neuroinflammatory processes, and (secondary) disruptions of neuronal Golgi apparatus and axonal transport. Apoptotic signaling through the receptor-mediated ('extrinsic') and mitochondria-based ('intrinsic') pathways demonstrates the key molecular players of apoptosis and the importance of the cysteine aspartate-special protease (caspase) cascade via interaction with different death domains and the role of effective caspase driving the execution of the cell death program. Diverse pathways lead to cell death. This is illustrated by the concept of the apoptosis-necrosis continuum, which integrates the various death pathways and subsequent intracellular signaling pathway ERS, ubiquitin-proteasome system (UPS), and ATP loss and explains the complex patterns of neuronal death (mix of PCD-types I, II, and/or III) (Nagley et al., 2010).

The role of mitochondria in generating ROS is well described by Abramov and coworkers (Abramov et al., 2010; Gandhi and Abramov, 2012). They examined changes in mitochondrial function in neurons differentiated from mouse embryonic stem-cell hybrids containing mitochondrial DNA polymorphic variants or mutations and found that in the neurons with complex I deficiency but not the complex IV defect, neuronal death was increased and was attenuated by ROS scavengers.

Mander and Brown (2005) demonstrated that in a mature mixed culture of neurons and glia, activation of inducible nitric oxide synthase (iNOS) or NADPH oxidase (NOX) alone does not result in substantial neuronal death but that simultaneous activation of both is synergistic in killing cocultured neurons. This neuronal death appears to be dependent on microglia, and microglial proliferation is itself stimulated by activating the NOX. These results suggest a dual-key hypothesis for inflammatory neurodegeneration, i.e. that activation of glial iNOS or NOX alone may be benign but when activated together they cause peroxinitrite ($ONOO^-$)-mediated neuronal death. Brown (2007) has posited that key mechanisms by which inflammatory-activated microglia and astrocytes kill neurons include iNOS, which is expressed in glia only during inflammation, and phagocytic NOX (PHOX) found in microglia and acutely activated by inflammation.

Several laboratories are investigating a mutation in the tRNA gene n-Tr20 as a genetic culprit behind the neurodegeneration observed in mice lacking GTPBP2, which is localized in the brain (Ishimura et al., 2014). This mutation is associated with 'stalling' when the GTPBP2 deficients encounter an aspartylglucosaminidase DNA triplet necessary for the production of proteins. This disruption can be overcome by an associated partner protein called GTPBP2. However, a complete knowledge of neurodegenerative diseases in humans is not known. In specific motor neuron degeneration, Imlach et al. (2012) and Lotti et al. (2012) have shown that aberrant splicing of Stasimon in cholinergic sensory neurons and interneurons leads to altered circuit function in this disorder. In this case, survival motor neuron (SMN) protein is lost, and residual SMN protein is insufficient to properly splice Stasimon transcript. This SMN deletion in cholinergic neurons causes an SMN-related phenotype by reducing the excitability of these neurons.

Neurodegenerative disorders, ischemic/nonischemic stroke, and PrD have a commonality in mechanism – oxidative and nitrosative stress

AD, PD, HD, and ALS are among the most commonly referred to neurodegenerative disorders (Navarro et al.,

2002; Anderson, 2004). They have mechanistic features in common, but they occur in different locations in the CNS. They also have some basis of origin in common with stroke, epileptic seizures, traumatic stress disorder, and schizophrenia. The frontal and parietal cortices and hippocampus in AD brain have increased protein carbonyl moieties, but not the cerebellum. Hydroxylated guanine is also increased in AD samples compared to age-matched controls. There is aggregation of protein as extracellular amyloid (βA) plaques and intracellular tau tangles. PD patients have a progressive loss of dopaminergic neurons in the substantia nigra and aggregation of the protein α-synuclein. PD brain is also characterized by reduced concentration of polyunsaturated free fatty acids in the substantia nigra, but the levels of lipid peroxidation markers (malondialdehyde and 4-hydroxynonenal) are increased.

What all these have in common is that these neurological disorders arise either early in life with a genetic factor or in the aging adult as a consequence of sustained oxidative and nitrosative stress as a result of superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), nitric oxide (NO), $ONOO^-$, hydroxyl ($HO^{\cdot}$), and singlet oxygen ($^-O_2$), which are kept in regulated steady-state concentrations (Navarro et al., 2002). It is important to recognize that the brain relies on mitochondrial energy for functioning comparable to or greater than the heart. Consequently, the brain is particularly susceptible to the radical ion products that arise as a result of normal function (Mariani et al., 2005; Gemma et al., 2007; Wang and Michaelis, 2010; Federico et al., 2012; Lopez-Erauskin et al., 2012). This is inconsequential in the normal course of events, but it becomes detrimental when sustained for a long period. Evidence indicates that mitochondrial energy metabolism underlies the pathogenesis of neurodegeneration, as decreased complex I activity is reported in the substantia nigra of postmortem samples obtained from patients with PD and impaired complex IV activity has been demonstrated in AD (Sriram et al., 1998; Calabrese et al., 2008). As already observed, free-radical-induced oxidative stress has been associated with the development of such disorders, and NO is among the key players with a central role. Catalysts scramble electron spin states to produce partially reduced forms of oxygen. Partially reduced forms of oxygen are highly active because the free radical is very unstable. It then must either accept or be a donor of electrons. Protein modification is initiated by reactions with $OH^{\cdot}$. The course of the oxidation process is also determined by the availability of O_2 and O_2^- or its protonated form hydroperoxyl ($HO^{\cdot}_2$) (Berlett and Stadtman, 1997). Collectively, these ROS can lead to oxidation of amino acid residue side chains, formation of protein-protein cross-linkages, and oxidation of the protein backbone, resulting in protein fragmentation. In addition, cytokines present in the normal brain are elevated in numerous pathological states, including PD, AD, multiple sclerosis (MS), ischemia, encephalitis, and viral infections of the CNS (Fischer and Maier, 2015). The involvement of cytokines is associated with the induction of nitric oxide synthase in the brain, a possible role for a glial derived NO in the pathogenesis of these diseases. However, oxidative stress has been associated with perturbations in thiol homeostasis (Hoshi and Heinemann, 2001; Chiu et al., 2014; Mukwevho et al., 2014) that may constitute the starting point for a vicious cycle leading to excessive $ONOO^{\cdot}$ generation in PD. The antioxidant enzymes SOD, catalase CAT, glutathione peroxidase (GPX), and glutathione reductase (GR), for example, display reduced activities in the brains of patients with AD. It is believed that free radicals of mitochondrial origin are among the primary causes of mitochondrial DNA (mtDNA) damage. Several studies have found increased levels of 8-hydroxy-2′-deoxyguanosine, a biomarker of oxidative DNA damage (Valavanidis et al., 2009), in mtDNA in the aged brain. In addition, oxidative stress, proinflammatory effects, presence of TNF and iNOS, and endothelial dysfunction have been found in this condition.

Neurodegenerative disorders differ in terms of location and expression

Heritable changes in gene expression that do not involve coding sequence modifications are referred to as ‘epigenetic.’ These modifications include DNA methylation and downstream modification of histones. Environmental factors, including heavy metals and dietary folate intake, perturb neurodegenerative genes by epigenetic means, leading to altered gene expression and late-onset neurodegenerative diseases (Kwok, 2010). AD and PD are two common neurodegenerative diseases that result in the progressive damage or death of neurons. Prusiner and associates (Mo et al., 2001) reported that downstream prion-like proteins (doppel, or Dpl), a paralog of the cellular prion protein, PrPC and PrPC, seem to have distinct physiologic roles. Dpl does not support prion replication as PrPC does. Overexpression of Dpl in the brain seems to cause a completely different neurodegenerative disease. There have been recent studies that show an association with long noncoding RNAs in neurodegenerative diseases, including AD, PD, HD, ALS, multiple system atrophy,

frontotemporal lobar degeneration, and glaucoma (Wan et al., 2017). A common link between the neurodegenerative diseases is chronic activation of innate immune responses, including those mediated by microglia, the resident CNS macrophages. Such activation can trigger neurotoxic pathways, leading to progressive degeneration (Amor et al., 2014).

Neurologic inflammatory component in astrocytes and glia

Microglia have a key role in the control of inflammatory processes, as well as tissue repair and regeneration. The adaptive immune response also plays important roles in resolving inflammation and mediating neuroprotection and repair. The involvement of astrocytes in the neuropathology of these diseases is likely a consequence of both the loss of normal homeostatic functions and gain of toxic functions. Intracellular aggregates in astrocytes are a common feature of various neurodegenerative diseases, and these aggregates perturb normal astrocytic functions in ways that can be harmful to neuronal viability (Phatnani and Maniatis, 2015). Several metals have been implicated in triggering or modulating immune responses, including the possibility of inflammatory neurodegeneration. Indeed, an animal model of PD uses the neurotoxin 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine to selectively injure nigrostriatal dopaminergic neurons (Amor et al., 2014). A characteristic of aging is the accumulation of advanced glycation endproducts, which is accelerated in MS, AD, and PD (Amor et al., 2014). Receptor for advanced glycation endproducts (RAGE) is increased in the AD-affected CNS, where it is expressed on neurons and astrocytes, and RAGE is expressed on oligodendrocytes in response to stress during MS. In addition, levels of HMGB1, a DNA-binding protein with proinflammatory properties, are increased in AD and PD as well as in MS. Several interesting reports have compared pathological gene expression in different patient groups, disease stages, and anatomical areas in ALS, PD, and AD. In ALS and PD, gene expression related to RNA splicing and protein turnover is disrupted, and several studies in ALS support the involvement of the cytoskeleton (Cooper-Knock et al., 2012). Gene expression profiling of RNA splicing and protein turnover is disrupted in ALS and PD. UPS in PD pathogenesis provided evidence of mitochondrial dysfunction in PD and AD and a possible role for dysregulation of intracellular signaling pathways, including calcium signaling in AD (Cooper-Knock et al., 2012). Methionine sulfoxide reductases (Msrs), MsrA and MsrB, are repair enzymes that reduce methionine sulfoxide residues in oxidatively damaged proteins to methionine residues in a stereospecific manner. These enzymes protect cells from oxidative stress and have been implicated in delaying the aging process and progression of neurodegenerative diseases (Kim and Gladyshev, 2007). Selenocysteine-containing forms of both MsrA and MsrB have been identified, and these are superior catalysts compared with cysteine-containing forms.

The brain relies greatly on mitochondria, as much as the heart does – or more

Mitochondria have a central role in aging-related neurodegenerative diseases (Lin and Beal, 2006). Mutations in mitochondrial DNA and oxidative stress both contribute to aging. Evidence indicates that mitochondrial dysfunction occurs early and acts causally in the pathogenesis of these diseases (Lin and Beal, 2006). However, mitochondrial genome is not the whole story. A great number of disease-specific proteins interact with mitochondria. Mitochondria play quite a large part in determining when a cell will die by ordinary cell death (necrosis) or programmed cell death (apoptosis). In apoptosis, the mitochondrion releases a molecule, cytochrome *c*, which can trigger apoptosis (Allen et al., 2008). We have noted that those suffering from PD or AD do have a higher mitochondrial mutation rate than do healthy people and so emphasizing the role of the functioning of mitochondria in these diseases (Fischer and Maier, 2015).

Neurological syndromes are the most frequent clinical presentations of mitochondrial disorders, a group of human diseases characterized by defects of the mitochondrial energy output. The respiratory chain is composed of five enzymatic multiheteromeric complexes (I, II, III, IV, and V), embedded in the inner membrane of mitochondria. The protein subunits of the respiratory chain complexes are assembled together and with prosthetic groups and metal-containing reactive centers by a set of chaperones and assembly factors, and coenzyme Q (a lipoidal quinone) and cytochrome c are also involved in mitochondrial respiration, serving as 'electron shuttles' between the complexes (Zeviani and Donato, 2004). The first two linked events of respiration are electron transfer and proton pumping. They are carried out by the mitochondrial electron transport chain (mETC). In humans,

complex I or NADH-ubiquinone oxidoreductase, which accomplishes the oxidation of NADH derived by the oxidation of fatty acids, pyruvate, and amino acids, contains seven subunits, which are encoded by the mtDNA (subunits ND1–ND6 and ND4L). Complex II or succinate-ubiquinone oxidoreductase, which accomplishes the oxidation of FADH2 derived from fatty acid and the Krebs cycle, is composed of only four subunits. Complex III or ubiquinol-ferricytochrome c oxidoreductase holds one subunit, cytochrome b. Complex IV or cytochrome c oxidase is composed of 13 subunits. The respiratory chain works as a proton pump that generates a proton gradient and a membrane potential of about 180 mV across the inner membrane, with a negative polarity at the matrix side of the inner membrane (Zeviani and Donato, 2004). The most common, and better characterized, early-onset mitochondrial encephalopathy is Leigh syndrome or subacute necrotizing encephalomyelopathy. However, molecular investigation fails to identify a gene defect in ~50% of adult patients affected by mitochondrial disease (Zeviani and Donato, 2004). Also, the mitochondrial genome is maternally inherited.

The energy demand of the brain is very large: it accounts for 20% of the body's energy consumption, even though its weight is less than 2% of the total body mass (Abou-Hamdan et al., 2011). Energy depletion is a major factor in the cascade of events culminating in dopaminergic neuronal death in PD. First, a frequent feature of the disease, there is an alteration of glucose metabolism. Second, there is a decrease in mitochondrial respiratory chain activity due to inhibition of the electron transport system complex I (NADH-ubiquinone oxidoreductase). Complex I activity is redox dependent and thiol regulated; therefore, its inhibition is associated with oxidative stress, and depletion of GSH, a major antioxidant and redox modulator, is observed in the substantia nigra of parkinsonian patients (Abou-Hamdan et al., 2011).

Mitochondria are unique organelles providing the host cell with ATP by oxidative phosphorylation. Mitochondria are also central to intracellular Ca^{2+} homeostasis, steroid synthesis, generation of free radical species, and forms of apoptotic cell death. Consequently, mitochondrial dysfunction has devastating effects on the integrity of cells and may thus be critically involved in aging, metabolic and degenerative diseases, as well as cancer in higher organisms and humans (Kann and Kovacs, 2007). The immense metabolic demand is because neurons are highly differentiated cells that need large amounts of ATP for maintenance of ionic gradients across the cell membranes and for neurotransmission. Neurons critically depend on mitochondrial function and oxygen supply, and their survival depends on mitochondria.

The brain contains high concentrations of polyunsaturated fatty acids (PUFAs) that are highly susceptible to lipid peroxidation. Consequently, it utilizes a higher amount of oxygen to produce energy compared to other tissues, but it is relatively deficient in antioxidant systems with low activity of GPX and catalase compared to other organs (Mariani et al., 2005). Neuronal mitochondria can be positioned and retained in neuronal segments with high metabolic demand, like active growth cones and presynaptic and postsynaptic structures (Kann and Kovacs, 2007). In excitable cells, the main mitochondrial Ca^{2+} extrusion pathway is the Na^{+}/Ca^{2+} exchanger, which is responsible for low resting Ca^{2+}. Neuronal activity is associated with Ca^{2+} entry via voltage-operated channels, receptor-operated channels, store-operated channels, and nonselective cation channels, as well as with Ca^{2+} release from the ER via receptors for IP3 and ryanodine (RyR) (Kann and Kovacs, 2007).

The activity of mitochondria in the electron transport chain produces oxidative stress products

The generation of ROS occurs at complexes I and III, as well as a-ketoglutarate dehydrogenase in the TCA cycle. Astrocytes are essential to providing precursors and other substrates to neurons, regulation of extracellular ion homeostasis, transport and metabolism of neurotransmitters, ammonia detoxification, and volume regulation. The underlying structural prerequisites of astrocytes are formation of an elaborated astrocytic network via gap junctions, close contacts to capillaries, and entrapment of synapses (Kann and Kovacs, 2007). Neuroinflammation and mitochondrial dysfunction are common features of chronic neurodegenerative diseases of the CNS. Both conditions can lead to increased oxidative stress by excessive release of harmful ROS and reactive nitrogen species (RNS), which further promotes neuronal damage and subsequent inflammation, resulting in a feed-forward loop of neurodegeneration (Fischer and Maier, 2015).

A common process associated with oxidative stress and severe mitochondrial impairment is the opening of the mitochondrial permeability transition pore, as described in many neurodegenerative diseases. X-linked adrenoleukodystrophy is caused by loss of function of the peroxisomal ABCD1 transporter, in which oxidative stress plays a pivotal role (Lopez-Erauskin et al.,

2012). Oxidative stress induced under galactose conditions leads to mitochondrial damage in the form of mitochondrial inner membrane potential dissipation, ATP drop, and necrotic cell death. These investigators show increased expression levels of cyclophilin D in the affected zones of brains in patients with adrenomyeloneuropathy, in the spinal cord of a mouse model of X-linked adrenoleukodystrophy (Abcd1-null mice), and in fibroblasts from patients with X-linked adrenoleukodystrophy. In unrelated work, it has been reported that mitochondrial ubiquitin ligase (MITOL) protects neuronal cells from mitochondrial damage caused by accumulation of S-nitrosylated MT-associated protein 1B-LC1 (Yonashiro et al., 2012). S-nitrosylation of LC1 induces a conformational change that serves both to activate LC1 and to promote its ubiquination by MITOL, indicating that MT stabilization by LC1 is regulated through its interaction with MITOL. Excessive NO production can inhibit MITOL. These investigators found that the balance between LC1 activation by S-nitrosylation and downregulation by MITOL is critical for neuronal cell survival. In addition, others have shown that in Drosophila pink1 and parkin mutants, defective mitochondria also give rise to ERS signaling, specifically to the activation of the protein kinase R-like ER kinase (PERK) branch of the UPR (Celardo et al., 2016). In addition, they found that genetic inhibition of dPERK-dependent ERS signaling and pharmacological inhibition using the PERK inhibitor GSK2606414 were neuroprotective in both pink1 and parkin Drosophila mutants. Finally, disturbance in mTOR signaling by a conserved serine/threonine kinase in the brain affects multiple pathways, including glucose metabolism, energy production, mitochondrial function, cell growth, and autophagy (Perluigi et al., 2015).

ERS that is elicited from the outer membrane elicits UPR and apoptosis

mTORC1 activation increases both oxygen consumption and mitochondrial number, and it controls mitochondrial oxidative function by positively regulating the activity of PGC1-α (PPARγ coactivator 1). Akt inhibits class O forkhead box transcription factors through direct phosphorylation and indirectly activates mTORC1. The central role played by mTOR signaling is in energy metabolism and autophagy, both of which are finely regulated by mitochondria (Perluigi et al., 2015).

Whether endogenously produced or taken up by diffusion, ROS have the potential to oxidize and unfold proteins, contributing to the damaging effects of oxidative stress. In some proteins, ROS transiently modulate protein activity, most commonly via the formation of sulfenic acids that lead to disulfide bonds (Cremers and Jakob, 2013). Sulfenic acids are generally considered to be highly unstable oxidation intermediates. They rapidly interact with nearby cysteines to form intermolecular or intramolecular disulfide bonds (R-S-S-R), making this the primary route for oxidant-mediated disulfide bond formation. ROS such as H_2O_2 are often transiently and locally produced as part of signaling processes, reversibly modulating redox-sensitive proteins in signaling pathways.

Dysfunction of the UPS is one of the major events that lead to the progression of neuronal loss. Aggregation of misfolded proteins has been attributed in the progression of various neurodegenerative diseases, such as AD, PD, and HD. In response to ROS, ubiquitin E3 ligases are key regulators involved in mediating the proteasomal degradation of misfolded proteins in the ER (Jha et al., 2014). ER has a role in the control of cellular essential parameters: protein folding, posttranslational modification, and proteostasis (Jha et al., 2014). Consequently, the UPS plays a vital role in regulated degradation of cellular proteins.

In many neurodegenerative disorders, such as AD, the brain has ubiquitinated protein inclusions, suggesting a role for ubiquitin-mediated proteasomal degradation of neuronal proteins. It has been shown that the b-amyloid fragment 1–40, in micromolar levels, causes the death of cortical neurons and induces the ubiquitination of several neuronal proteins (Favit et al., 2000). Prevention of ubiquitination and inhibition of proteasome activity blocked the neurotoxic effect of b-amyloid. The researchers concluded that b-amyloid neurotoxicity may cause toxicity through the activation of protein degradation via the ubiquitin-proteasome pathway.

Oxidative protein folding: the disulfide bond

Oxidative protein folding refers to a process involving both the formation of disulfide bonds and a conformational folding reaction. This physicochemical process results in the formation of a fully folded and biologically mature disulfide-bond-containing protein (Narayan, 2012). The oxidative regeneration of the biopolymer that takes place in the ER requires a balanced oxidizing redox potential via a favorable oxidized/reduced glutathione (GSSG/GSH) ratio that facilitates the formation of disulfide bonds (Narayan, 2012). The antioxidant enzymes SOD, Cat, GPX,

and GR, for example, display reduced activities in the brains of patients with AD (Gemma et al., 2007). Understanding the relationship between proteostasis and aging has provided important insights into neurodegeneration (Douglas and Dillin, 2010), and conditional knockout of autophagy genes (ATGs) can cause neurodegeneration in the absence of disease mutations.

The ER is a cellular organelle in which secretory and membrane proteins are synthesized and modified, and it also functions as an intracellular calcium store. There may be accumulation of unfolded protein from the breaking of disulfide bonds that are critical for tertiary protein structure. The proteins in the lumen of the ER induce a series of adaptive responses (Wang et al., 2009). GRP78 has a role in this to regulate ERS-signaling pathways. This leads to UPR survival and apoptosis responses. In this process, there are three main ER-transmembrane signaling molecules: ATF6, IRE1, and PERK (Hoshi and Heinemann, 2001; Wang et al., 2009). These are maintained in an inactive state with ER-associated caspases (murine caspase-12 = human caspase 4) through binding to GRP78. After protein misfolding is caused by ERS, GRP78 is titrated away. This activates the survival pathways to block further damage (Wang et al., 2009). A knock-in mouse model expresses a mutant form of GRP78 that has a deletion of the ER-retrieval sequence KDEL. The mutant mice have a neurologic phenotype of reeler mutant-like malformation characterized by disordered layer formation in the cerebral cortex and cerebellum. This is accompanied by reduced brain size and protein level. It is of some interest that reelin and its mRNA are significantly reduced in patients with schizophrenia, and epigenetic aberration of the human reelin gene is associated with psychiatric disorders (Wang et al., 2009).

PERK, ATF6, and IRE1 are characterized by having distinct cytosolic functions associated with the ability to activate their respective transducers: ATF4, cleaved ATF6, and Spliced sXBP1. This results in their effect on protein translation, cellular metabolism, and cell survival or cell death programs. In the first case, PERK inhibits general protein translation (via eIF2α phosphorylation). This enables translation of transcripts harboring an alternate open reading frame, including ATF4, a key transducer. ATF4 is implicated in the induction of several ATGs and can activate cell death programs (in cooperation with CHOP). The IRE1 RNAse domain mediates splicing and activation of the transcription factor XBP-1. As a result, chaperones induce the ERAD components, and proteins involved in lipogenesis (Senft and Ronai, 2015). These three ERS sensors, double-stranded RNA activated PERK, ATF6, and IRE1, activate a complex transcriptional cascade with distinct cytosolic functions. PERK phosphorylates eIF2a to decrease overall translation while increasing the specific translation of genes including ATF4. On ERS, ATF6 is translocated to and is processed at the Golgi apparatus to create a highly active transcription factor. IRE1 decreases overall protein flux to the ER (Senft and Ronai, 2015).

Cells undergo apoptosis when ERS is excessive or prolonged. The UPR acts to alleviate ERS by (i) increasing folding capacity, (ii) inhibiting general protein translation, and (iii) promoting the degradation of misfolded proteins (Hoshi and Heinemann, 2001). Apoptosis is expressed with the expression of CHOP, an apoptotic transcription factor 4,5, or the activation of ER-specific caspases (Hoshi and Heinemann, 2001). The three sensors, IRE1, PERK, and ATF6, are activated dependent on the dissociation of GRP78 ER chaperone protein in response to ERS (Hoshi and Heinemann, 2001; Senft and Ronai, 2015). Finally, the UPR acts to alleviate ERS by increasing folding capacity, inhibiting general protein translation and promoting the degradation of misfolded proteins, but if the response is unable to rescue cells, the ERS will eventually lead to cell death (caspase-mediated apoptosis) (Hoshi and Heinemann, 2001; Senft and Ronai, 2015).

Apoptosis works in synchrony with autophagy

The activation of the double-stranded RNA activated PERK-eIF2α-ATF4 pathway results in up-regulation of the expression of a large set of ATGs. While IRE1 signaling has been implicated in promoting autophagy (via c-JNK-mediated signaling), it also elicits negative regulation of autophagy. Functionally, autophagy promotes cell survival, increases energy supply, and mediates innate immune responses. A loss of ATGs induces the UPR by a negative feedback mechanism. Autophagy may decrease cellular stress levels by removal of ER membranes, which contain UPR sensors, or decreasing the amplitude of stress by clearing aberrant proteins from the ER (Senft and Ronai, 2015).

Methionine and cysteine are essential S amino acids that are important in the double bond

Sulfur is an important element in biological systems. This atom is usually integrated into proteins as the redox-active cysteine residue and in molecules such as GSH,

thioredoxin (TRX), and glutaredoxin, which are vital antioxidant molecules and are therefore essential for life (Mukwevho et al., 2014). There are a number of proteins responsible for maintaining an intracellular reducing environment, including glutathione, TRX, and glutaredoxin. Glutaredoxins form part of the TRX fold family of proteins, and its three-dimensional structure consists of four internally located β-sheets surrounded by three α-helices (Mukwevho et al., 2014). A deficiency in GRX1 results in loss of mitochondrial membrane potential and has been implicated in neurodegenerative diseases such as PD and motor neuron diseases. Glutaredoxin catalyzes the reduction of protein mixed disulfides with GSH and hence helps to prevent oxidative stress. Glutathione is an example of a thiol-containing nonprotein that works in concert with GPXs and glutathione S-transferases in the reduction of peroxides, and it forms mixed glutathione-adducts which reduce disulfide bonds. TRX and glutaredoxin are thiol-containing proteins responsible for the reduction of disulfide bonds intracellularly through the formation of a TRX/glutaredoxin-protein intermediate. Disulfide bonds stabilize the monomeric protein slowing down the population of aggregation-prone conformations, and they mediate the formation of aggregates. Disulfide bonding enzymes (like protein disulfide isomerases [PDIs]) are up-regulated in the presence of protein aggregation as a general response to cellular stress and UPR activation. They may interact specifically with the aggregating proteins. PDIs assist disulfide bonding, and they promote protein folding and minimize protein misfolding and aggregation (Mossuto, 2013).

Proteins are very sensitive to oxidative modifications, particularly methionine and cysteine residues. Disulfide bond formation has the potential to mediate extensive yet fully reversible structural and functional changes, reflecting adjustment to the prevailing oxidant levels. Cysteines contain a polarizable sulfur atom, and their oxidation state can range from the fully reduced thiol/thiolate anion to the fully oxidized sulfonic acid (Cremers and Jakob, 2013). Most reactions of thiols in biochemical systems involve the nucleophilic attack of the deprotonated thiolate anion (RS^-) on an electrophilic center, hence making the overall reactivity of a thiol group strongly dependent on the pKa value of the cysteine side chain. ROS may modulate protein activity via the formation of sulfenic acids that lead to disulfide bonds (Cremers and Jakob, 2013). When reactive cysteine thiols meet reactive oxygen, nitrogen, or chlorine species, sulfenic acid formation occurs. Sulfenic acids are unstable oxidation intermediates, and they rapidly interact with nearby cysteines to form disulfide bonds (R-S-S-R), making this the primary route for oxidant-mediated disulfide bond formation (Cremers and Jakob, 2013). Sulfenic acids also react with the small tripeptide glutathione, leading to S-gluthathionylation. The ability of proteins to use reversible disulfide bond formation as a functional switch requires high reactivity of the participating cysteine thiols (i.e. low p*K*a), close proximity to other cysteines, and sufficient disulfide-mediated conformational rearrangements to affect the function of the protein. This is very favorable in cysteine-coordinating zinc (Zn^{2+}) centers, where the positive charges of Zn^{2+} serve to stabilize the reactive thiolates.

Elevated circulating concentration of the sulfur containing amino acid homocysteine, hyperhomocysteinemia, produces complex changes within the blood vessel wall. In the peripheral circulation, these changes include oxidative stress, proinflammatory effects such as expression of TNF, iNOS, and endothelial dysfunction. Studies in cystathionine-β-synthase-deficient mice revealed that very modest hyperhomocysteinemia produces hypertrophy and altered mechanics in the cerebral microcirculation. Hyperhomocysteinemia-induced oxidative stress may occur as a result of decreased expression and/or activity of key antioxidant enzymes as well as increased enzymatic generation of $O_2^{\cdot-}$ (the precursor for multiple reactive oxygen and RNS) (Faraci and Lentz, 2004). Homocysteine is formed upon the demethylation of methionine, and an elevated level of homocysteine is associated with AD (Hoshi and Heinemann, 2001). While homocysteine induces ERS, homocysteine-induced ERS-responsive protein has been shown to enhance presenilin (PS)-mediated amyloid β production.

GSH deficiency or a decrease in the GSH/GSSG ratio manifests itself largely through an increased susceptibility to oxidative stress. Just as low intracellular GSH levels decrease cellular antioxidant capacity, elevated GSH levels generally increase antioxidant capacity and resistance to oxidative stress. In fact, GSH plays a central role in cell death, including apoptotic cell death. GSH levels influence caspase activity, transcription factor activation, BCL2 expression and function, ceramide production, thiol-redox signaling, and phosphatidylserine (PtdS) externalization (Ballatori et al., 2009). In addition, CNS dysfunction has been observed in all diseases related to inborn errors of GSH metabolism. Patients with AD had increased oxidation of red blood cells; glutathione is correlated with the cognitive status of the patients (Ballatori et al., 2009). The significance of GSH depletion in PD is suggested by the death of dopaminergic cells in Drosophila models with Parkin mutation. The loss of GSH in the substantia nigra may be related to selective cell death in nigral dopaminergic cells. It has been argued that a disturbance of glutathione

homeostasis may either lead to or result from oxidative stress in neurodegenerative disorders. An important role for glutathione was proposed for the pathogenesis of PD, because a decrease in total glutathione concentrations in the substantia nigra has been observed in preclinical stages (Schulz et al., 2000). PD provides the best evidence for a dysfunction of glutathione metabolism.

Deposition of insoluble fibrillary protein

Abnormal interactions between proteins that result in aberrant intracellular and extracellular deposition of self-aggregating misfolded proteins with the formation of high-ordered insoluble fibrils are common pathological hallmarks of multiple neurodegenerative disorders. The protein deposits in neurological diseases are generally dense fibrillar structures containing a high percentage of β-pleated sheet secondary structure. The deposits are generally ubiquitinated and may contain numerous cellular proteins (Schulz et al., 2000). These inclusion bodies that are generally fibrillar contain a high percentage of β-pleated sheet secondary structure. It has been suggested that the conversion to an insoluble protein may involve a change in the three-dimensional structure of the protein, possibly by the formation of a stable β-pleated sheet via a polar zipper or possibly by CAG trinucleotide repeat coding for polyglutamine (Kaytor and Warren, 1999). It has been observed that polyglutamine expansion, missense mutation, protein modification, or damage may lead to protein misfolding. Finally, ubiquitinated aggregates could sequester components of the degradation machinery, in such manner influencing general neuronal protein degradation. Then an imbalance between neuronal protein synthesis and degradation would exist that could have downstream effects resulting in or accelerating neurodegeneration (Kaytor and Warren, 1999). Many proteins have been identified that interact with expanded polyglutamine-containing proteins.

It has been reported that the effects of an L-methionine-enriched diet in wild-type mice produced changes in brain structure and function. The animals presented (1) higher levels of phosphorylated tau protein, (2) increased levels of amyloid-β (Aβ) peptides, including the formation of Aβ oligomers, (3) increased levels of inflammatory response, (4) increased oxidative stress, (5) decreased level of synaptic proteins, and (6) memory impairment and loss. They also observed dysfunction of the Wnt signaling pathway (Tapia-Rojas et al., 2015). Moreover, a reduction in the protein levels of the Wnt target genes cyclin-D1 and c-jun was observed, which indicated a decrease in the activity of the entire Wnt signaling pathway. These investigators suggest that L-methionine induces a loss of Wnt signaling function, a situation reminiscent of what has been observed in AD (Tapia-Rojas et al., 2015).

UPR under continued stress leads to protein agglomeration and obstruction of the ER canal

Oxidative regeneration of the biopolymer takes place within the ER by a favorable GSSG/GSH ratio, which facilitates the formation of disulfide bonds. Proteins that are destined for the PM or are secreted outside the cell often contain disulfide bonds and fold oxidatively. They are processed within the environs of the ER prior to being secreted (Narayan, 2012). ER protein folding often involves disulphide bond formation, which occurs through the electron shuffling reactions catalyzed by the PDI family members. ER oxidoreductin 1 (Ero1) catalyzes the oxidation of PDI by linking disulphide formation with the reduction of oxygen to generate H_2O_2. It now seems that H_2O_2 provides a source of ROS in the ER (Cyr and Hebert, 2009).

ER is essential to regulating proper protein folding, posttranslational modification, and subsequent protein trafficking to maintain normal cellular homeostasis. However, the accumulation of toxic proteins in the brain leads to impairment of the UPS machinery, and it leads to the progression of neuronal loss. Neurons depend on the proper functioning of E3 ligases and UPS to maintain neuronal homeostasis. Improper or loss of function of UPS in affected neurons results in protein aggregation with oxidative stress, ERS, and ultimately, neuronal death (Jha et al., 2014). PDI is a disulfide bond-modulating ER chaperone that facilitates the ERAD of misfolded proteins (Jaronen et al., 2014). PDI prevents SOD1 aggregation, and its inactivation increases ERS. When PDI is activated, NOX is activated, and this leads to increased $O_2^{\bullet-}$ production and associated neurotoxicity (Jaronen et al., 2014). In microglia cells, ROS production depends on NOX associated with PDI to regulate its function. Overexpression of PDI promotes NOX activation in vascular smooth muscle cells, and furthermore, NOX activation directly correlates with PDI expression levels. On the other hand, excessive protein misfolding is the penalty of oxidative stress that exceeds ER adaptive capabilities in neuronal cells and cause aberrant NOX activation in microglia.

Accumulation of misfolded proteins in excessive amounts overwhelms the 'cellular quality control' system, resulting in impaired protective mechanisms designed to promote correct folding and degrade faulty proteins (Rao and Bredesen, 2004). The degradation of cellular proteins is coupled, via the ubiquitin-mediated proteasomal degradation pathway, to ER dislocation of many ER substrates. Conditions that block ER retrotranslocation of proteins and/or proteasome function and degradation may result in their accumulation within the ER. These may be deposited as inclusion bodies or plaques within cells or in extracellular spaces. There are several factors that lead to neurotoxicity. They are inhibition of synaptic function, loss of synpases leading to disruption of neuronal functions, sequestration of critical cellular chaperones and vital transcription factors by misfolded proteins, interference with numerous signal-transduction pathways, alteration of calcium homeostasis, release of free radicals and consequent oxidative damage, dysfunction of the protein degradation pathway through the UPS, and/or induction of cell-death proteases leading to programmed cell death (Rao and Bredesen, 2004).

The molecular basis of HD has been shown to be the polyglutamine (polyQ) expansion in the N terminus of Htt, a cytosolic protein expressed in almost all cells of the body. The cytoplasmic accumulation of polyQ triggers ERS by inhibiting the UPS, leading to activation of both the TNF receptor-associated factor 2 (TRAF2)-ASK1 complex and caspase-12-mediated apoptotic pathways (Rao and Bredesen, 2004).

Ubiquitination is a reversible reaction

Ubiquitin molecules are removed by deubiquitinase (DUB) to be recycled before polyubiquitinated proteins are degraded in the proteasome. Moreover, the percentage of ubiquitinated proteins present in the cell at any time is determined by changes in the activity of DUBs. Glutamate stimulation decreased the total DUBs activity in hippocampal neurons, but it had no effect on the activity of Uch-L1. This indicated that not all DUBs are affected. These results indicate that excitotoxic stimulation with glutamate has multiple effects on the UPS. Finally, impairment of DUBs activity involves specific DUBs such as those associated with the proteasome (Caldeira et al., 2013).

The ERS response activates a number of signaling pathways from the ER to the cytosol and nucleus. First, the UPR, which compensates damage, triggers the synthesis of chaperons to refold the unfolded proteins and to inhibit global protein translation. Second, ERAD breaks up unfolded proteins at the proteasome (Gulyaeva, 2015).

UPR signaling occurs in three parallel branches

The upstream UPR components activate prosurvivial mechanisms (e.g. through transcription of GRP78, PDI, and sarco/ER Ca^{2+} ATPase 2b), and proapoptotic mechanisms (e.g. through activation of JNKs, caspase-12, and C/EBP transcription), thus confirming the pleiotropic character of UPR (Gulyaeva, 2015).

The ER resident BiP (Hsp70) binds the luminal tails of PERK, ATF6, and IRE1 to suppress their activity. When the levels of unfolded protein are elevated, BiP is titrated away, enhancing PERK-dependent phosphorylation of eIF2α, which leads to the suppression of protein synthesis and the activation of the transcription factor ATF4. Concomitantly, IRE1 is activated to mediate the expression of Xbp1/Hac1, which drives a global transcriptional induction of chaperones and quality control factors that maintain unfolded protein levels within a narrow range. When the stress that triggers UPR is chronic or extremely severe, PERK signaling drives the ATF4-dependent expression of the transcription factor CHOP, and its downstream products trigger apoptotic cell death (Cyr and Hebert, 2009; Senft and Ronai, 2015; Gulyaeva, 2015).

The removal of H_2O_2 from cells is facilitated by catalase, GSH and TRX peroxidases, and other nonenzymatic means. ER-localized peroxiredoxin metabolizes the H_2O_2 produced by Ero1. In addition, Cyr and Hebert (2009) showed that H_2O_2 is indeed produced by Ero1 *in vivo*, thereby providing the first indication of a mechanism for the disposal of ER-generated H_2O_2. HSF1 is acetylated at a key residue required for DNA binding, and SIRT1 deacetylates this site to activate HSF1. SIRT1 is activated by NAD to levels that increase in response to ROS and other metabolic conditions (Cyr and Hebert, 2009).

ERAD is initiated on the recognition of nonnative terminally misfolded or unassembled proteins, which are sorted to an ER-membrane-associated dislocation/ubiquitination complex containing adaptor proteins that recognize the quality control receptor and/or the ERAD substrate directly. Cytosolic components are recruited to retrotranslocation complexes to aid in the extraction of the ERAD substrate from the ER (Cyr and Hebert, 2009).

Protein S-nitrosation takes place on specific cysteine residues. These cysteines covalently incorporate a NO moiety to form S-nitrosothiol derivatives. The process

depends on the ratio between NO produced by NO synthases and nitrosothiol removal. Many cysteine-containing proteins are found to undergo S-nitrosation. The enzymes catalyzing ubiquitination, mainly ubiquitin E3 ligases and the 20S component of the proteasome, may be redox modulated (Rizza et al., 2014).

The transmission of neural signal is through calcium channels and the gap (synapse) involving CaCMM kinase(s) and Na^+,K^+-ATPase

Substantial evidence indicates that gap junctions and hemichannels have pathologic roles in various neurologic diseases. For instance, dysfunction and dysregulation of gap junctions and hemichannels in glial cells play a significant role in neuroinflammation in the CNS. This results in neuronal damage. Blocking gap junction (BGJ) hemichannel significantly suppressed neuronal loss of the spinal cord and extended survival in transgenic mice carrying human SOD1 in an ALS mouse model (Takeuchi et al., 2011). Moreover, this blockage of BGJ hemichannel improved memory impairments in double transgenic mice expressing human amyloid precursor protein in AD mouse models. Investigators synthesized a novel gap junction hemichannel blocker INI-0602 using dihydropyridine conjugates as a chemical drug delivery system. Dihydropyridine conjugates had a favorable feature of INI-0602 BBB penetration, CNS retention, and low toxicity. However, INI-0602 treatment did not significantly alter Aβ load despite cognitive improvement. In another study, inactivation or hyperactivation of *N*-methyl-D-aspartate (NMDA) receptors induces neuronal cell death in primary hypothalamic cultures, specifically during the peak of developmental gap junction coupling. They report a critical role of neuronal gap junctions in cell death caused by increased or decreased NMDA receptor function in developing neurons (Vaccari et al., 2007).

It has been reported that reductions in Na^+,K^+ ATPase activity in AD tissue may result from the direct effects of amyloid on this enzyme. These studies used dual immunolabeling an absence of Na^+,K^+ ATPase staining in a zone surrounding congophilic plaques that was occupied by dystrophic neurites. In addition, cerebral Na^+,K^+ ATPase activity could be directly inhibited by high concentrations of soluble Aβ (Dickey et al., 2005). They concluded that disruption of ion homeostasis and osmotic balance may interfere with normal electrotonic properties of dendrites, blocking intraneuronal signal processing, and contribute to neuritic dystrophia.

Intracellular Ca^{2+} accumulation caused by the activation of glutamate receptors boosting synaptic activity is a key factor in triggering neuronal apoptosis (Orellana et al., 2011). Up-regulation of Ca^{2+} extrusion abolishes its development. This effect can be initiated by concentrations of ouabain that are within the range of an endogenous analog, suggesting a novel functional role for Na^+,K^+-ATPase in neuroprotection. This suggests a functional role for Na^+,K^+-ATPase in neuroprotection. The occupation by ouabain of its binding site on Na^+,K^+-ATPase results in an acceleration of Ca^{2+} extrusion and prevents Ca^{2+} accumulation in cytoplasm. The inhibition of the NCX abolishes the neuroprotective effects of ouabain by preventing Ca^{2+} extrusion and it induces Ca^{2+} overload. This makes ouabain binding ineffective.

Connexin hemichannels are the precursors of gap junction

Connexin hemichannels are the precursors of gap junction channels (GJCs) that are formed by two hemichannels provided by one of each apposed cells. A hemichannel is formed by six connexins that oligomerize laterally, leaving a central pore. Connexins are highly conserved proteins (Sibarov et al., 2012). The hemichannels are potential regulators of the beginning and maintenance of homeostatic imbalances present in diverse brain diseases. A constant increase in induced Ca^{2+}i mediated by augmented Ca^{2+} entry through hemichannels that are permeable to Ca^{2+} and deficient or insufficient Ca^{2+} handling by injured cells could lead to cell death. Receptor stimulation leads to activation of phospholipase C (PLC) and formation of cytoplasmic IP3, which promotes the release of Ca^{2+} stored in the ER. Both IP3 and Ca^{2+} diffuse to neighboring cells through GJC generating waves of rises in induced intracellular Ca^{2+} concentration. The increase in free induced Ca^{2+} induced by IP3 and P2X receptor opening could promote ATP release through Cx43 (connexin) and Px1 hemichannels, extending the Ca^{2+} wave to neighboring cells. Astrocytes release glutamate and ATP via Cx43 hemichannels, which can activate more microglia and could promote activation of relevant neuronal receptors and further opening of hemichannels in neurons (Sibarov et al., 2012). Activated microglia might release glutamate and ATP through hemichannels, while astrocytes could release the same molecules

through Cx43 hemichannels. This gliotransmission activates neuronal purinergic and NMDA receptors, resulting in an elevation of the intracellular free Ca^{2+} concentration that might trigger massive Cx36 and Panx1 hemichannel opening and further neuronal death. Dysfunction of astroglial, microglial hemichannels, and GJC is commonly elicited in those brain diseases that are associated with inflammatory responses.

The atrophic and degenerative processes in the neurons of AD, PD, ALS, HD, and SCA patients are invariably accompanied by alterations in calcium homeostasis (Bezprozvanny, 2010). Moreover, the calcium hypothesis states that this deregulation of calcium signaling is one of the early-stage and key processes in the pathogenesis of these diseases. The Ca^{2+} channels that are involved in neuronal Ca^{2+} signaling includes the voltage-dependent Ca^{2+} channels of the PM, NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, transient receptor potential channels, and depot-controlled channels. IP3Rs and RYR are mediators of release of Ca^{2+} from the intracellular ER depot (Bezprozvanny, 2010).

The Ca^{2+} level in the cytosol is maintained in a very narrow range by the sarcoplasmic/ER calcium ATPase (SERCA) pump in the ER, the Ca^{2+} pump of the PM, and the Na^{+}/Ca^{2+} exchanger of the PM. The MCU is an ion channel involved in the rapid and massive entrance of calcium into the mitochondria. Ca^{2+}-binding proteins also maintain a level of Ca^{2+} in the cytosol (such as calbindin-D28, calretinin, and parvalbumin) and inside the ER (such as calreticulin and calnexin) in neurons. In addition, neurons have many Ca^{2+}-dependent structures, such as proteins that carry out the fusion of synaptic vesicles with the presynaptic membrane (such as synaptotagmins), Ca^{2+}-dependent kinases and phosphatases (such as the Ca^{2+}/CaM kinase and the Ca^{2+}-dependent phosphatase calcineurin), Ca^{2+}-dependent signaling enzymes (such as Ca^{2+}-dependent adenylate cyclase), and Ca^{2+}-dependent transcription factors. In addition, an excess of Ca^{2+} in the cytosol leads to the capture of Ca^{2+} by the mitochondria via MCU. This induces the opening of mitochondrial permeable transit pore (mPTP) and apoptosis. The direct interaction between mutant Htt and the mitochondria is also disrupted (Bezprozvanny, 2010).

Ca^{2+} equilibrium is disrupted in AD

Aβ forms by sequential cleavage of the β-amyloid precursor-protein (β) by the γ-secretase (γ). Aβ also forms oligomers. These integrate into the PM and form pores permeable to Ca^{2+}-ions. The binding of Aβ with the surface PtdS and Ca^{2+}-mediated damage of mitochondria cause a decrease in the ATP level, leading to the transfer of PtdS from the inner to the outer surface of the PM. Glutamate activates mGluR1/5 receptors. The production of InsP3 is increased. This facilitates InsP3-mediated release of Ca^{2+} from the ER. PS function as channels for Ca^{2+} drain from the ER and HAD related mutations disrupt the Ca^{2+} drain function of PS. PS can modulate the activity of InsP3R, RyanR, and the SERCA pump. The increase in cytosolic Ca^{2+} concentration suppresses long-term potentiation, which leads to modification of the neuronal cytoskeleton, the loss of synapses, and axon atrophy. The excessive amount of Ca^{2+} in the mitochondria appears due to the activity of MCU, and it leads to the opening of the mPTP and apoptosis (Bezprozvanny, 2010). An effect of the Aβ oligomer accumulation is the excessive levels of Ca^{2+} in the neuronal cytosol and the expression of mutant PS characteristic of AD. An inhibitor of the NMDA receptor called memantine has been approved for AD treatment.

Cellular stress in schizophrenia

Throughout the past couple of decades, schizophrenia remained elusive in almost all of its aspects; its definition changed not less than 40 times, the etiology remains unclear, and its management is changing continuously (Jansson and Parnas, 2007). According to the National Institute of Health, schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. Patients basically experience hallucinations, delusions, thought disorders, movement disorders, reduced feeling of pleasure, reduced speaking, and troubles in cognitive functions. These symptoms are usually classified as positive, negative, and cognitive.

Schizophrenia's etiology is thoroughly researched today. It shows associations with genetics, fetal growth, hypoxia, infections, childhood antecedents, substance use, life experiences like social adversity, environmental and cellular stressors, and even seasonal change. However, all these factors somehow add up to changes in the brain macrostructure and microstructure, which alter the perception of reality as if the brain sends perceptions along the wrong path, creating false conceptions. Throughout this article, the focus is on cellular-level stressors in schizophrenia.

Multiple clinical trials have measured levels of ROS and proved an association between high levels and schizophrenia in different cell types. A recent meta-analysis

suggests that oxidative stress is a prospect biomarker for the pathophysiology and clinical course of schizophrenia (Flatow et al., 2013). A recent research was done with a new cell model based on patient-derived cells from the human olfactory mucosa. Samples were taken from healthy controls and schizophrenic patients (and other psychiatric patients). This research proved alterations of genes axin 2 (AXIN2), cadherin 2 (CDH2), GSK3 β, integrin subunit alpha 8 (ITGA8), integrin subunit β 1 binding protein 1 (ITG β 1BP1), PI3R1 regulatory subunit 1, PP2 regulatory subunit B β (PPP2R2β), WNT5A, regulator of G protein signaling (RGS4), gamma-aminobutyric acid type A receptor epsilon subunit (GABRE), LDL-receptor-related protein 8 (LRP8), solute carrier family 1 member 1 (SLC1A1), parvin β (PARV β), laminin subunit alpha 3 (LAMA3), and reelin (RELN) signaling in neurons. Also, alteration in gene expression pathways like ephrin receptor signaling, NRF2-mediated oxidative stress response, axonal guidance signaling, IL-8 signaling, virus entry via endocytic pathways, semaphorin signaling in neurons, Fc-receptor-mediated phagocytosis in macrophages and monocytes, glutathione metabolism (which was found to be depleted in post-mortem samples), and vitamin D receptor/retinoid X receptor activation (Matigian et al., 2010).

Recent studies have also implicated RNS in the pathophysiology of schizophrenia. NO plays important roles in different body systems. In the brain, it is responsible for regulating synaptic plasticity, neurotransmitter release, and neurodevelopment (Bitanihirwe and Woo, 2011). Especially important for schizophrenia is its role as a second messenger of the NMDA receptor activation, which interacts with both dopaminergic and serotonergic pathways (Dietrich-Muszalska et al., 2015). These pathways have been suggested to be also involved in the pathogenesis of schizophrenia.

Another suggested way of RNS effect on dopamine is through one of its metabolites, $ONOO^-$, a relatively long-lived cytotoxic oxidant through nitration of tyrosine residues in proteins to form 3-nitrotyrosine (Antunes et al., 2005). It is suggested that RNS, as ROS, can modify proteins and nucleic acids, induce lipid peroxidation, and decrease antioxidant levels and auto-oxidation of dopamine (Dietrich-Muszalska et al., 2015). This is further supported by other studies that measured protein nitration by measuring levels of 3-nitrotyrosine, which were higher in the prefrontal cortex of schizophrenic patients (Andreazza et al., 2010). It is also suggested that RNS can be involved in DNA damage through influencing the activation of transcription factor NF-κB (Dietrich-Muszalska et al., 2015).

Oxidative stress seems to play another role in schizophrenia through mitochondrial dysfunction (Morris and Berk, 2015). Various mitochondrial abnormalities were described in schizophrenia like ultrastructural abnormalities in mitochondria, evidence to shift in energy production via glycolysis, mitochondrial dysfunction in peripheral immune cells, mitochondria DNA damage, damage to the electron transport chain, and high lactate in brain or cerebrospinal fluid. However, mitochondrial dysfunction could be also genetically inherited, and this is currently researched in mitochondrial complex I activity (Andreazza et al., 2010). These findings could be explained by the important role of mitochondria on neuronal plasticity (Mattson, 2007).

Brain-derived neurotrophic factor (BDNF) is another recently suggested biomarker for schizophrenia (Green et al., 2011). BDNF is a neurotrohin that affects neurogenesis, neuroplasticity, neuronal survival, differentiation, and growth. Low levels of BDNF show a strong association with altered synaptic connectivity in schizophrenic patients and may be responsible for the psychotic signs and symptoms. It has been shown that this is due to altered BDNF mRNA and protein in the prefrontal cortex in schizophrenic patients.

Genes are also prospect biomarkers; hence, scientists have tried relentlessly to research different genes to prove their association with schizophrenia. Hundreds of papers were published but not with consistent data. Therefore, a research group has created a database 'SzGene' (Allen et al., 2008). Through systematic reviews and random effect meta-analyses, they could describe different genetic polymorphisms and 24 genetic variants in 16 different genes that showed significant statistical association with schizophrenia. However, further research is still needed in genetics to really allow us to use it in tackling schizophrenia.

An exciting new research approach to schizophrenia is through proteomes. It also searches for biomarkers through varied techniques like two-dimensional polyacrylamide gel electrophoresis, two-dimensional difference gel electrophoresis, shotgun sequencing, and other various techniques through using samples from post-mortem brain tissue, blood, and plasma. This research increased exponentially in the past years to hopefully find candidate biomarkers for diagnosis and potential treatment turning points in schizophrenia (Nascimento and Martins-de-Souza, 2015). Differentially expressed proteins were found in neuronal transmission, synaptic function, calcium hemostasis and signaling, energy metabolism, cytoskeleton, oxidative stress, immune system, and inflammation. A more recent meta-analysis stated that the most common proteins proven to be altered in schizophrenia are aldolase C, glial fibrillary acidic protein, and astrocytic proteins (Davalieva et al., 2016).

An ER protein, sigma-1 receptor, is a novel ligand-operated ER chaperone that regulates bioenergetics, free radical generation, oxidative stress, UPR, and cytokine signaling (Hayashi, 2015). This receptor could be the missing link between the transformation of psychological stress into cellular stress. Psychological stress also triggers the formation of cytokines, which in turn stimulates inflammatory response. It is now widely accepted that inflammation and oxidative stress go hand in hand as well.

Inflammation is a protective response of the body toward injury or infection. This is mediated through different cells, immunoglobulins, and cytokines. Neuroinflammation is quite similar, but one major difference is microglial activation (Kirkpatrick and Miller, 2013). Following injury or the exposure to proinflammatory signals such as interferon (IFN)-γ and TNF-α or psychological stress (Howes and McCutcheon, 2017), microglia are activated and release proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IFN-γ, or chemokine c-x-c motif) ligand and lipid mediator prostaglandin E2. Microglial activation in turn activates astrocytes, which further release proinflammatory cytokines and chemokines (Trepanier et al., 2016). However, levels of proinflammatory signals, cytokines, and chemokines were varied across different studies, and limitations to form a valuable meta-analysis exist.

Microglial activation leads to excessive synaptic pruning and loss of cortical grey matter especially in stress-sensitive areas like the prefrontal cortex and hippocampus. These changes could elucidate the cognitive and negative symptoms (Howes and McCutcheon, 2017). Furthermore, cortical affection could lead to dopaminergic dysregulation, which can elucidate the psychotic symptoms. This is also enhanced with evident changes in dopaminergic receptor density noticed in schizophrenic patients (Arreola et al., 2016). Moreover, microglial reaction to stressors might be genetically affected as well. This further accentuates the genetic role in schizophrenia.

Some inflammatory cytokines like TNF-α and IFN-γ are cytotoxic to oligodendrocytes, and they are also responsible for abnormal expression of mRNA for myelin basic protein (Buntinx et al., 2004). Oligodendrocytes are highly susceptible to oxidative stress as they have low levels of levels glutathione, GPX, and mitochondrial manganese SOD, which are antioxidant defense mechanisms. Oxidative stress can damage myelin through peroxide and HO· radical, which react with the PUFAs in myelin and further disturb neuronal connections. Moreover, five genes that are responsible for oligodendrocyte myelin formation were found to be down-regulated in schizophrenia (Hakak et al., 2001). These mechanisms mainly target myelin; hence, white matter is also affected in schizophrenia.

One more mode of communication in the brain that may be affected in schizophrenia is the excitatory pathway via glutamatergic neurons (Coyle). These are also responsible for regulating neuronal migration, neurite outgrowth, synaptogenesis, and the 'pruning' of neurons by apoptosis. Through postmortem research of brain samples from schizophrenic patients, it was hypothesized that this is due to reduced function of the NMDA subtype of glutamate receptor. However, it is debatable which subunit of the receptor is responsible.

Another common finding in postmortem samples in schizophrenia and other neurodegenerative diseases is abnormally high levels of iron. This is injurious to dopamine neurons and induces formation of free radicals (Hetz et al., 2007b). Moreover, abnormally high levels of homocysteine, hyperhomocysteinaemia, can cause oxidative stress through auto-oxidation of homocysteine to form ROS, increased lipid peroxidation, and reduced production of GPX (Bitanihirwe and Woo, 2011). These metabolic changes also contribute to the pathogenesis of schizophrenia. These varying mechanisms prove how elusive the pathogenesis and, hence, the treatment of schizophrenia could be. Further research is needed in all the aforementioned mechanisms.

Conclusion

The PERK branch of UPR and its downstream signaling pathway offer extremely rich subjects for research in the context of neurodegenerative diseases and targeting therapeutic treatment. Simply, this is due to the contradictory and sometimes unpredicted effects on disease pathophysiology and disease progression. It is unclear how much PERK contributes to neurodegenerative diseases. It is not an easy task owing to the crosstalk with other important stress responses involved in neuroprotection, such as autophagy. Hence, it becomes extremely convincing to carefully and systematically assess PERK signaling to distinct neurodegenerative diseases.

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