Biometals (2012) 25:837–845
DOI 10.1007/s10534-012-9544-8

Iron and ER stress in neurodegenerative disease

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Received: 29 December 2011 / Accepted: 22 March 2012 / Published online: 12 April 2012

Abstract Neurodegenerative disease is a condition in which subpopulations of neuronal cells of the brain and spinal cord are selectively lost. A common event in many neurodegenerative diseases is the increased level of endoplasmic reticulum (ER) stress caused by accumulation and deposits of inclusion bodies that contain abnormal aggregated proteins. However, the basis of how ER stress contributes to the selective neuronal vulnerability and degeneration remain elusive. Iron accumulation in the central nerve system is consistently present in many neurodegenerative diseases. In the past 5 years we have begun to show a relationship between polymorphisms in the HFE (high iron) gene and the risk of neurodegenerative disorders. Recent findings have suggested a connection between ER stress and iron metabolism and neurodegeneration. Here we review how the different levels of chronic ER stress contribute to the different fates of neurons, namely the adaptive response and neuronal death. And, we discuss the roles of iron and HFE genotype in selective neuronal vulnerability and degeneration through modifying the ER stress level.

Keywords Iron · Chronic ER stress · Adaptive response · Neurodegeneration

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Introduction

The proper functioning of the endoplasmic reticulum (ER) is critical for numerous aspects of cell physiology. Accordingly, the ability to respond to perturbations in ER function, called ER stress, is a fundamentally important property of all cells. ER stress includes the accumulation of unfolded, misfolded or excessive protein, alterations in calcium storage, ER lipid or glycolipid imbalances, or changes in the redox or ionic conditions of the ER lumen (Ron and Walter 2007). The ER responds to the accumulation of unfolded proteins in its lumen by activating intracellular signal transduction pathways, collectively called the unfolded protein response (UPR). UPR provokes a series of transcriptional activities to increase protein folding capacity in the ER and to reduce the protein load entering the ER. Although UPR is usually a short-term homeostatic mechanism and necessary for cell survival, prolonged ER stress activates apoptotic cell death pathways (Lin et al. 2007). ER stress has been implicated in many neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis and prion diseases. However, the exact contributions to and casual effects of ER stress in neuron degeneration are not clear (Lindholm et al. 2006). Furthermore, it is not known why in the same subpopulation some neurons are selectively vulnerable to cell death and others are more resistant; even though they are harboring the

same ER-stress-inducing mutations (Saxena and Caroni 2011).

In addition to genetic influences, environmental factors such as viral infection, hypoxia and drug exposure can induce ER stress (Rutkowski and Kaufman 2007). Metal ions available in the diet and atmosphere are known to impact neurodegeneration. We have previously reviewed the role of metal ions, especially iron, copper and zinc in several neurodegenerative disorders (Zecca et al. 2004). Emerging therapeutic interventions to limit neurodegeneration have been developed by using chelating compounds to alleviate or redistribute metal ions (Badrick and Jones 2011). A relationship between ER stress and iron metabolism has been suggested including an effect of mutations in a hemochromatosis protein (HFE) that is involved in cellular iron uptake (de Almeida et al. 2007b; Liu et al. 2011). An increased frequency of these HFE polymorphisms has been found in individuals with neurodegenerative diseases (Nandar and Connor 2011). In the light of these recent findings, a new research area is developing around the roles of iron and HFE in neurodegeneration and ER stress. This relationship is significant because HFE polymorphisms are the most common gene variant in Caucasians and the presence of the HFE mutant protein has been shown to impact a range of cellular functions such as glutamate release (Mitchell et al. 2011), cholesterol metabolism (Ali-Rahmani et al. 2011), and oxidative stress (Lee et al. 2007);all popular targets for therapeutic strategies. ER stress is observed in cells with HFE mutations and in animals with an HFE mutation (Liu et al. 2011). Thus, it can be logically predicted that ER stress and its role in neurodegenerative processes will be influenced by HFE genotype. This review is designed to serve as an overview from which to launch this new area of investigation.

Overview of ER stress

The ER stress response, UPR, is initiated when the accumulation of misfolded proteins sequesters the ER chaperon binding protein (BiP) away from the luminal domain of three ER stress transducers and leads to their activation (Bertolotti et al. 2000). Each activated transducer, namely inositol-requiring protein-1(IRE1), protein kinase RNA-like ER kinase (PERK) and activating transcription factor-6 (ATF6) defines a distinct branch of the UPR. IRE1 is a transmembrane kinase/endoribonuclease (RNase) that, upon activation, initiates the nonconventional splicing of X-box binding protein 1 (XBP-1) mRNA (Calfon et al. 2002; Yoshida et al. 2001). Spliced Xbp-1 (Xbp-1s) mRNA encodes a transcription activator that drives transcription of genes such as ER chaperones, whose products directly participate in ER protein folding (Lee et al. 2003). Besides the survival effector XBP-1s, IRE activates pro-apoptotic IRE1–TRAF2 (tumor necrosis factor receptor associated factor 2)-JNK (Jun amionterminal kinase) pathway during prolonged ER stress (Hetz et al. 2006; Urano et al. 2000; Ventura et al. 2006; Xia et al. 1995). IRE may also contribute to degradation of membrane-associated mRNA through RIDD (regulated IRE1 dependent decay), which may lead to apoptosis in the setting of severe ER stress (Hollien et al. 2009; Hollien and Weissman 2006). A second branch is mediated by PERK, a transmembrane kinase that phosphorylates the eukaryotic translation initiation factor 2 subunit α (eIF2α), thereby reducing protein synthesis and counteracting ER protein overload (Harding et al. 1999). eIF2α phosphorylation also allows the selective translation of some mRNAs that lead to the production of transcription activators such as activating transcription factor-4 (ATF4) (Harding et al. 2000). ATF4 increases the expression of its key downstream target, C/EBP-homologous protein (CHOP) which mediates ER-stress-induced apoptosis by suppressing the pro-survival protein B-cell lymphoma 2 (Bcl-2) (McCullough et al. 2001) or increasing the transcription of ER oxidase 1α (ERO1α) (Marciniak et al. 2004). Other pro-apoptotic mechanisms of CHOP pathway include up-regulation of growth arrest and DNA-damage-inducible protein-34 (GADD34) and death receptor-5 (DR5) (Tabas and Ron 2011). A third branch involves the transcription factor ATF6. Upon activation, the ATF6 cytoplasmic domain (ATF6f) is liberated from its membrane anchor by regulated proteolysis. ATF6 has a major role in chaperone induction and can also transcriptionally induce CHOP (Ye et al. 2000). The three branches collaborate to activate UPR target genes to control the cell's response to ER stress, by promoting both cell survival and pro-apoptotic pathways. Besides the pro-apoptosis pathways of the UPR, the proteases caspase family also plays an important role in ER-induced-apoptosis. Some of them appear to be relatively specific to ER stress, such as ER-localized

caspase-12 or -4 (Nakagawa et al. 2000), and others feed into general caspase cascade pathways. These activated caspases in turn activate caspase-3, -6 and -7, initiating degradation of vital elements and cell death (Chowdhury et al. 2008; Malhi and Kaufman 2011).

During ER stress, all three branches of the UPR are activated. Each branch promotes both pro-survival and pro-apoptotic pathways. Thus, a central paradox of the UPR is that it facilitates both cell protective and cell death responses (Rutkowski and Kaufman 2007). How does the UPR switch between the adaptive and cell death fates? One of the mechanisms is that the timing of activation can differ (DuRose et al. 2006). In particular, prolonged ER stress leads to the sequential deactivation of the IRE1, ATF6 and PERK pathways, respectively. Down-regulation of IRE1, coupled with maintenance of PERK signaling may drive the cell death (Lin et al. 2007). Secondly, in a cell culture system, adaption is favored during mild ER stress as a consequence of the selective instability of pro-apoptotic mRNAs and proteins. In this context, the expression of ER chaperons, such as BiP is persistent wherein CHOP expression is modest and transient (Rutkowski et al. 2006).

ER stress can be acute or chronic in nature (Kaufman 2002; Marciniak and Ron 2006). The examples of acute stress include hypoxia and/or ischemia, calcium depletion and glucose deprivation. Cells need only to tolerate these acute insults for relatively brief durations (on the order of minutes to hours) and clear the ER of accumulated unfolded proteins in that time by a rapid activation and readily deactivation of the UPR (Rutkowski and Kaufman 2007). By contrast, chronic stresses require quasi-permanent changes in ER function. Chronic stresses that activate the UPR can encompass: genetic mutations that lead to persistent ER perturbations; viral infection; various neurodegenerative disorders of protein aggregation; several liver diseases and the normal physiological conditions in some cells, such as immune cells, endocrine and paracrine cells, and hepatocytes (Kaufman 2002; Malhi and Kaufman 2011). Chronic ER stress can be persistently tolerated from days to years so that, even if cell death occurs to a small extent, the majority of cells will ultimately survive and adapt to the stress, a condition called adaptive ER stress. Failure to adapt to chronic ER stress can induce widespread pathologic apoptosis (Kaufman 2002).

Iron and ER stress

Suggestive evidence for crosstalk between iron metabolism and ER stress has been emerging. By gene expression screening, increased levels of ER chaperons BiP and calreticulin (CRT) was found in iron-burdened astrocytoma (Ye and Connor 2000). Proteomic analysis revealed an increased hepatic BiP expression in dietary iron-loaded mice (Petrak et al. 2007). ER stress might be underlie the down-regulation of haptoglobin, a glycoprotein produced mainly by the liver and secreted into the circulation in mice fed on an iron enriched diet for 3 weeks. These studies raise a possible link between dietary intake of iron and iron-induced ER stress (Faye et al. 2007). Free or unbound iron can serve as a pro-oxidant. Ferrous iron (Fe^{2+}) catalyzes the conversion of reactive oxygen species to highly reactive hydroxyl radical ($^{\bullet}OH$) via Fenton reaction, while ferric iron (Fe^{3+}) can react with superoxide ($O_2^{\bullet-}$) and generates Fe^{2+}, leading to $^{\bullet}OH$ formation via the Haber–Weiss reaction. Excess iron can induce oxidative stress by protein peroxidation, lipid peroxidation, and DNA oxidation (Salvador 2010; Salvador and Oteiza 2010). The antioxidant quercetin effectively blocked iron-induced increase in CRT expression (Nunez et al. 2001). Thus, concurrent hypotheses propose that iron overload increases oxidative stress which in turn activates ER stress by releasing CRT and other ER proteins (Oliveira et al. 2011). Moreover, ER stress may in turn modulate iron metabolism as down regulation of the iron mobilizing protein transferrin as reported in stable transfectants of CHOP, an apoptotic ER stress marker (You et al. 2003). Two recent papers corroborated the relationship of iron and ER stress by showing that both in hepatocyte-derived cells and in mouse liver, ER stress inducers reshaped the expression of iron-related genes, namely ferroprotein and ferritin H, through induction of hepcidin, which controls plasma iron levels and perhaps innate immunity (Oliveira et al. 2009; Vecchi et al. 2009). ER stress impairs the processing of cell surface proteins, including histocompatibility complex class 1 (MHC-1) proteins of which HFE is a member (Feder et al. 1998), from the ER to cell surface (de Almeida et al. 2007a; Granados et al. 2009). Thus once initiated it is clear to envision a cycle of ER stress and iron dys-homeostasis which would include interfering with the assembly and cell surface expression of HFE protein. In addition to iron,

other metal ions, such as copper and lead have been reported to induce ER stress in the cancer cell lines (Gandin et al. 2012; Shinkai et al. 2011). The evidence for copper and ER stress has had limited investigations.

HFE and ER stress

HFE is a major MHC-I protein and mutations in the protein are associated with cellular iron overload. However, unlike other MHC-1 proteins, the HFE protein does not function as an antigen-presenting molecule (Feder et al. 1996). The major function of the HFE protein is to regulate iron homeostasis. The HFE protein interacts with β_2 microglobulin (β_2m) in the ER and is transported to the plasma membrane (Feder et al. 1998; Feder et al. 1997; Waheed et al. 1997) where the HFE protein forms a stable complex with the transferrin receptor (TfR) (Feder et al. 1998). HFE binds to TfR at or near the Fe- holotransferrin (i.e. Fe–Tf) binding site where it can competitively inhibit Tf binding to the TfR (Lebron et al. 1999). Therefore, the HFE protein functions in the regulation of iron homeostasis by binding to the TfR and reducing the transport of Fe–Tf molecules.

HFE protein has a wide tissue expression (Holmstrom et al. 2003), including the brain (Zecca et al. 2004). The two most common polymorphisms are known as C282Y and H63D (Feder et al. 1996). Both C282Y and H63D mutations alter the HFE repressor function for Tf–Fe uptake and could result in increased cellular uptake of iron and iron deposition (Feder et al. 1998; Lee et al. 2007). The C282Y mutation prevents the assembly of HFE protein with β_2m and forms protein aggregates in the ER (Waheed et al. 1997). In cell lines over-expressing HFE C282Y, ER retention of the mutant protein elicits UPR activation. Moreover, chemical chaperons reducing ER stress can decrease the mutant protein aggregating by facilitating its degradation (de Almeida et al. 2007b). In an inducible expression cell model developed from a human neuronal cell line SH-SY5Y, the other and more common HFE mutant protein, H63D activates the UPR. This response is followed by a persistent ER stress, as the signals of UPR sensors attenuate, they are followed by up-regulation of Caspase-3 cleavage and activity. Furthermore, these in vitro findings are recapitulated in a transgenic mouse model carrying *Hfe* H67D, the mouse equivalent of the human H63D mutation. In this model, UPR activation is detected in the lumbar spinal cord at 6-month then declines at 12-month in association with increased Caspase-3 cleavage (Liu et al. 2011). It is worth noting that mutant HFE H63D protein does not aggregate in the ER (Feder et al. 1998; Liu et al. 2011), thus this mutant protein itself does not causes ER stress as a mis-folded protein. Instead, it may induce ER stress by perturbation of calcium homeostasis (Mitchell et al. 2011) or disturbance in lipid metabolism (Schröder 2007). In addition, both HFE mutants are associated with a higher level of oxidative stress in the cells (Lee et al. 2007), which also could result in ER stress activation (Gregersen and Bross 2010).

HFE is necessary for regulation of hepcidin expression; a protein that is involved in regulation of cellular iron export. Hepatocyte-specific expression of HFE by recombinant adeno-associated virus in WT and HFE knock-out mice both increased HFE and hepcidin mRNA and lowered hepatic iron levels (Gao et al. 2010). Studies are underway to examine the effect of mutant HFE proteins on hepcidin expression and explore the correlation among HFE, ER stress, hepcidin and iron which should reveal the delicate relationship between iron regulation and vital cellular pathways.

ER Stress and neurodegenerative disease

ER stress has been reported in various neurodegenerative diseases. However, the exact contributions to and casual effects of ER stress in neuron degeneration are not clear (Lindholm et al. 2006). ER stress markers have been observed in degenerating tissues, and it has been proposed that an overloaded ER promotes cell death (Marciniak and Ron 2006; Yang et al. 2001). In ALS, for example, studies in familial ALS mutant SOD1 mice have demonstrated that UPR is activated, peaks and declines selectively in vulnerable motor neurons prior to their denervation, suggesting ER stress might be the early cause for motor neuron degeneration (Saxena et al. 2009). On the other hand, there are reports suggesting that ER stress could protect against or delay the onset of neurodegenerative diseases. For example, mild ER stress caused by a mutation in an ER chaperon protects photoreceptor neurons from various death stimuli in adult *Drosophila* (Mendes et al. 2009). The active-form of one ER

stress marker XBP1 protein has protective effects against cell death induced by 1-methyl-4-phenylpyridinium (MPP+) and proteasome inhibitors. Moreover, the exogenous expression of the active-form XBP1 protein by adenoviral vectors significantly suppresses the degeneration of dopaminergic neurons in the mouse model of PD (Sado et al. 2009). These observations may suggest mild ER stress promotes cell survival, representing an adaptive response (Rutkowski et al. 2006), whereas ER stress at a higher, chronic level may induce widespread pathologic apoptosis (Kaufman 2002). Thus, in neurons, chronic but very mild ER stress may be present and well-tolerated when the adaptive response of UPR is favored. Physiologically or artificially increasing the high level of pro-survival ER stress effectors, such as BiP, spliced XBP1 may have a protective effect on neuron survival (Mendes et al. 2009) and could be therapeutically valuable. However, even at a modest level, chronic ER stress can lead to increased neuronal vulnerability and degeneration when present for many years in a terminally differentiated cell such as a neuron. It is our opinion that genetic and environmental influences, or the combination of such influences that would occur in the presence of an HFE mutation and iron exposure through dietary and environment could combine over a number of years to promote neuronal cell death where individually they would be sub-lethal Thus, the HFE genotype in combination with iron exposure through diet (carnivores versus vegans) and environment (e.g. miners, etc.) could be prototypic model of gene and environment interaction on neurodegenerative processes.

Although different casual effects of ER stress in neurodegeneration can be explained by the different level of stress, this scenario seems to not fully explain an important feature of neurodegenerative diseases—selective neuronal vulnerability. Even in the same subpopulation, some neurons are selectively vulnerable to cell death and others are more resistant, though they are harboring the same ER-stress-inducing mutations (Saxena and Caroni 2011). This observation suggests the neighboring non-neuronal cells play an important role in neuron cell death, a process called non-cell-autonomous toxicity (Ilieva et al. 2009). As a means of integrating these observations, we propose a model of ER stress combined with environmental insults that can lead to selective neuronal death. The model is that mild chronic ER stress still increases host susceptibility to disease because over time, additional insults from the external environment or from the neighboring non-neuronal cells may integrate and increase the ER stress level, transform the adaptive ER stress response to an apoptotic process and eventually lead to neurodegeneration. The selective vulnerability of the particular neuronal subpopulations depends on where and when the additional insults occur. Using neuronal cells and mild pharmacological perturbation, we found a chronic and adaptive ER stress response could be transformed to apoptosis by non-ER-stress insults from the environment, at least partially through increased level of ER stress (Liu and Connor, unpublished data). It would be very interesting to examine whether iron overload could increase the ER stress load to reach the apoptosis threshold in the neurons harboring mild ER stress (Fig. 1).

Persistent and mild, but chronic ER stress may be encountered physiologically. One example is in our HFE H63D expressing cells where prolonged ER stress is observed without neuronal cell degeneration. The *Hfe* H67D knock-in mice appear to grow normally and are fertile, producing homozygous offspring in the number expected (Tomatsu et al. 2003). No gross behavior defects are detected in these mice, despite selective activation of UPR in the lumbar spinal cord at 6-month of age (Liu et al. 2011). This expression of ER stress indicates this model can be used to study chronic damage of affected neurons in neurodegenerative diseases. The model is consistent with the human population studies where H63D is a genetic modifier for ALS. The frequency of this polymorphism is as high as 30 % in sporadic ALS patients compared to 14 % in the control populations (Connor and Lee 2006; Goodall et al. 2005; He et al. 2011; Restagno et al. 2007; Sutedja et al. 2007; Wang et al. 2004). The C282Y polymorphism has been linked to PD (Dekker et al. 2003; Guerreiro et al. 2006) and multiple sclerosis (Ristic et al. 2005). In AD, the data for HFE and risk of disease are more mixed possibly reflecting the gene/environment interaction (Connor and Lee 2006). When HFE mutations are considered along with apoE4 mutations in AD, however, the data that HFE genotype impacts AD is stronger (Alizadeh et al. 2009; Combarros et al. 2003; Pulliam et al. 2003). These data are consistent with observations that HFE genotype alters cholesterol and lipid status (Ali-Rahmani et al. 2011).

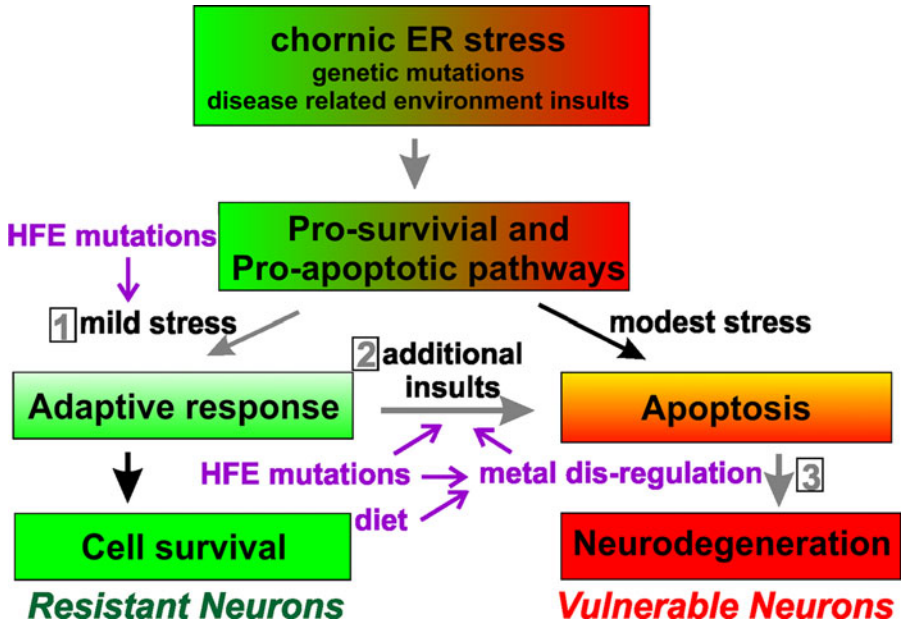

Fig. 1 Model of the roles of chronic ER stress, HFE mutations and metal in neurodegeneration Chronic ER stress activates both pro-survival and pro-apoptotic pathways in all neurons. It may result in either adaptive response then cell survival fate, or apoptosis and cell death fate, depends on the level of the stress. We propose that selective neuronal vulnerability is the consequences of two strikes of the insults that eventually lead to neurodegeneration as indicated by *gray arrows*: genetic mutations or disease related environment insults may set the mild ER stress predispositions and can be well-tolerated in neurons (*1*). Additional insults from the neighboring cells or the environment may increase the ER stress level and transform the adaptive response to apoptosis (*2*) and cause neuron dysfunction and death (*3*). The selective vulnerability of the particular neuronal subpopulations depends on where and when the additional insults occur. HFE mutations may help to establish an intrinsic permissive ER stress in neurons or operate as an additional insult to increase the ER stress level to reach the degeneration thresholds. Metal dis-regulation including from diet may act as an important environmental insult, which could drive disease at all stages

Conclusion

Metal dysregulation, especially involving iron and copper has been observed in various neurodegenerative diseases (Zecca et al. 2004). Emerging evidence is accumulating and compelling that implicates a cross-talk between iron metabolism and ER stress. ER stress is already under evaluation as a key contributor in various neurodegenerative diseases (Lindholm et al. 2006). But, ER stress activates both cell survival and cell death pathways. Therefore, chronic ER stress, depending on its level, may result in adaption or apoptosis (Rutkowski and Kaufman 2007; Tabas and Ron 2011). Differences in host susceptibility can occur because of genotypic differences that may predispose neurons to stress because they harbor disease-relevant mutations or insults that increase or decrease susceptibility. Moreover, the different levels of ER stress could lead to selective neuronal cell death as seen in neurodegenerative diseases because insults from neighboring cells or the environment may have a major impact on increasing ER stress load in neurons and regional differences in the brain can be expected from environmental stress; perhaps depending on metabolic activity of different brain regions or targets of environmental toxins. For example, ALS may occur more frequently in athletes who may increase metabolic activity of motor neurons over less active population (Sutedja et al. 2009). The substantia nigra is selectively targeted by neurotoxins associated with PD. Eventually, as the ER stress reaches a certain threshold, that is lower in HFE expressing neurons, it increases the vulnerability in particular neurons and causes degeneration. Metal dys-regulation may act as an important environmental insult, which could drive disease at all stages. Therefore the correlation between ER stress, and HFE mutations in our cell and animal models (Liu et al. 2011) support the argument that

HFE mutations are risk factors for many neurodegenerative diseases (Nandar and Connor 2011). Especially in the case of H63D, the presence of ER stress may help to establish an intrinsic permissive ER stress in neurons that operates as an additional insult to increase the ER stress level to reach the degeneration thresholds (Fig. 1). The models that have been developed to study HFE mutations will serve as a valuable tool to open a new promising avenue in ER stress, metal regulation and neurodegeneration research.

References

Ali-Rahmani F, Hengst JA, Connor JR, Schengrund CL (2011) Effect of HFE variants on sphingolipid expression by SH-SY5Y human neuroblastoma cells. Neurochem Res 36: 1687–1696

Alizadeh BZ, Njajou OT, Millan MR, Hofman A, Breteler MM, van Duijn CM (2009) HFE variants, APOE and Alzheimer's disease: findings from the population-based Rotterdam study. Neurobiol Aging 30:330–332

Badrick AC, Jones CE (2011) Reorganizing metals: the use of chelating compounds as potential therapies for metal-related neurodegenerative disease. Curr Top Med Chem 11:543–552

Bertolotti A, Zhang Y, Hendershot LM, Harding HP, Ron D (2000) Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. Nat Cell Biol 2:326–332

Calfon M, Zeng H, Urano F, Till JH, Hubbard SR, Harding HP, Clark SG, Ron D (2002) IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. Nature 415:92–96

Chowdhury I, Tharakan B, Bhat GK (2008) Caspases—an update. Comp Biochem Physiol B Biochem Mol Biol 151: 10–27

Combarros O, Garcia-Roman M, Fontalba A, Fernandez-Luna JL, Llorca J, Infante J, Berciano J (2003) Interaction of the H63D mutation in the hemochromatosis gene with the apolipoprotein E epsilon 4 allele modulates age at onset of Alzheimer's disease. Dement Geriatr Cogn Disord 15: 151–154

Connor JR, Lee SY (2006) HFE mutations and Alzheimer's disease. J Alzheimers Dis 10:267–276

de Almeida SF, Fleming JV, Azevedo JE, Carmo-Fonseca M, de Sousa M (2007a) Stimulation of an unfolded protein response impairs MHC class I expression. J Immunol 178: 3612–3619

de Almeida SF, Picarote G, Fleming JV, Carmo-Fonseca M, Azevedo JE, de Sousa M (2007b) Chemical chaperones reduce endoplasmic reticulum stress and prevent mutant HFE aggregate formation. J Biol Chem 282:27905–27912

Dekker MC, Giesbergen PC, Njajou OT, van Swieten JC, Hofman A, Breteler MM, van Duijn CM (2003) Mutations in the hemochromatosis gene (HFE), Parkinson's disease and parkinsonism. Neurosci Lett 348:117–119

DuRose JB, Tam AB, Niwa M (2006) Intrinsic capacities of molecular sensors of the unfolded protein response to sense alternate forms of endoplasmic reticulum stress. Mol Biol Cell 17:3095–3107

Faye A, Ramey G, Foretz M, Vaulont S (2007) Haptoglobin is degraded by iron in C57BL/6 mice: a possible link with endoplasmic reticulum stress. Blood Cells Mol Dis 39:229–237

Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R Jr, Ellis MC, Fullan A et al (1996) A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nat Genet 13:399–408

Feder JN, Tsuchihashi Z, Irrinki A, Lee VK, Mapa FA, Morikang E, Prass CE, Starnes SM, Wolff RK, Parkkila S et al (1997) The hemochromatosis founder mutation in HLA-H disrupts beta2-microglobulin interaction and cell surface expression. J Biol Chem 272:14025–14028

Feder JN, Penny DM, Irrinki A, Lee VK, Lebron JA, Watson N, Tsuchihashi Z, Sigal E, Bjorkman PJ, Schatzman RC (1998) The hemochromatosis gene product complexes with the transferrin receptor and lowers its affinity for ligand binding. Proc Natl Acad Sci USA 95:1472–1477

Gandin V, Pellei M, Tisato F, Porchia M, Santini C, Marzano C (2012) A novel copper complex induces paraptosis in colon cancer cells via the activation of ER stress signaling. J Cell Mol Med 16:142–151

Gao J, Chen J, De Domenico I, Koeller DM, Harding CO, Fleming RE, Koeberl DD, Enns CA (2010) Hepatocyte-targeted HFE and TFR2 control hepcidin expression in mice. Blood 115:3374–3381

Goodall EF, Greenway MJ, van Marion I, Carroll CB, Hardiman O, Morrison KE (2005) Association of the H63D polymorphism in the hemochromatosis gene with sporadic ALS. Neurology 65:934–937

Granados DP, Tanguay PL, Hardy MP, Caron E, de Verteuil D, Meloche S, Perreault C (2009) ER stress affects processing of MHC class I-associated peptides. BMC Immunol 10:10

Gregersen N, Bross P (2010) Protein misfolding and cellular stress: an overview. Methods Mol Biol 648:3–23

Guerreiro RJ, Bras JM, Santana I, Januario C, Santiago B, Morgadinho AS, Ribeiro MH, Hardy J, Singleton A, Oliveira C (2006) Association of HFE common mutations with Parkinson's disease, Alzheimer's disease and mild cognitive impairment in a Portuguese cohort. BMC Neurol 6:24

Harding HP, Zhang Y, Ron D (1999) Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. Nature 397:271–274

Harding HP, Novoa I, Zhang Y, Zeng H, Wek R, Schapira M, Ron D (2000) Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol Cell 6:1099–1108

He X, Lu X, Hu J, Xi J, Zhou D, Shang H, Liu L, Zhou H, Yan B, Yu L et al (2011) H63D polymorphism in the hemochromatosis gene is associated with sporadic amyotrophic lateral sclerosis in China. Eur J Neurol 18:359–361

Hetz C, Bernasconi P, Fisher J, Lee AH, Bassik MC, Antonsson B, Brandt GS, Iwakoshi NN, Schinzel A, Glimcher LH, Korsmeyer SJ (2006) Proapoptotic BAX and BAK modulate the unfolded protein response by a direct interaction with IRE1alpha. Science 312:572–576

Hollien J, Weissman JS (2006) Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. Science 313:104–107

Hollien J, Lin JH, Li H, Stevens N, Walter P, Weissman JS (2009) Regulated Ire1-dependent decay of messenger RNAs in mammalian cells. J Cell Biol 186:323–331

Holmstrom P, Dzikaite V, Hultcrantz R, Melefors O, Eckes K, Stal P, Kinnman N, Smedsrod B, Gafvels M, Eggertsen G (2003) Structure and liver cell expression pattern of the HFE gene in the rat. J Hepatol 39:308–314

Ilieva H, Polymenidou M, Cleveland DW (2009) Non-cell autonomous toxicity in neurodegenerative disorders: ALS and beyond. J Cell Biol 187:761–772

Kaufman RJ (2002) Orchestrating the unfolded protein response in health and disease. J Clin Invest 110:1389–1398

Lebron JA, West AP Jr, Bjorkman PJ (1999) The hemochromatosis protein HFE competes with transferrin for binding to the transferrin receptor. J Mol Biol 294:239–245

Lee AH, Iwakoshi NN, Glimcher LH (2003) XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. Mol Cell Biol 23: 7448–7459

Lee SY, Patton SM, Henderson RJ, Connor JR (2007) Consequences of expressing mutants of the hemochromatosis gene (HFE) into a human neuronal cell line lacking endogenous HFE. FASEB J 21(2):564–576

Lin JH, Li H, Yasumura D, Cohen HR, Zhang C, Panning B, Shokat KM, Lavail MM, Walter P (2007) IRE1 signaling affects cell fate during the unfolded protein response. Science 318:944–949

Lindholm D, Wootz H, Korhonen L (2006) ER stress and neurodegenerative diseases. Cell Death Differ 13:385–392

Liu Y, Lee SY, Neely E, Nandar W, Moyo M, Simmons Z, Connor JR (2011) Mutant HFE H63D protein is associated with prolonged ER stress and increased neuronal vulnerability. J Biol Chem 286:13161–13170

Malhi H, Kaufman RJ (2011) Endoplasmic reticulum stress in liver disease. J Hepatol 54:795–809

Marciniak SJ, Ron D (2006) Endoplasmic reticulum stress signaling in disease. Physiol Rev 86:1133–1149

Marciniak SJ, Yun CY, Oyadomari S, Novoa I, Zhang Y, Jungreis R, Nagata K, Harding HP, Ron D (2004) CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. Genes Dev 18: 3066–3077

McCullough KD, Martindale JL, Klotz LO, Aw TY, Holbrook NJ (2001) Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state. Mol Cell Biol 21:1249–1259

Mendes CS, Levet C, Chatelain G, Dourlen P, Fouillet A, Dichtel-Danjoy ML, Gambis A, Ryoo HD, Steller H, Mollereau B (2009) ER stress protects from retinal degeneration. EMBO J 28:1296–1307

Mitchell RM, Lee SY, Simmons Z, Connor JR (2011) HFE polymorphisms affect cellular glutamate regulation. Neurobiol Aging 32:1114–1123

Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J (2000) Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. Nature 403:98–103

Nandar W, Connor JR (2011) HFE gene variants affect iron in the brain. J Nutr 141:729S–739S

Nunez MT, Osorio A, Tapia V, Vergara A, Mura CV (2001) Iron-induced oxidative stress up-regulates calreticulin levels in intestinal epithelial (Caco-2) cells. J Cell Biochem 82:660–665

Oliveira SJ, Pinto JP, Picarote G, Costa VM, Carvalho F, Rangel M, de Sousa M, de Almeida SF (2009) ER stress-inducible factor CHOP affects the expression of hepcidin by modulating C/EBPalpha activity. PLoS ONE 4:e6618

Oliveira SJ, de Sousa M, Pinto JP (2011) ER stress and iron homeostasis: a new frontier for the UPR. Biochem Res Int 2011:896474

Petrak J, Myslivcova D, Man P, Cmejla R, Cmejlova J, Vyoral D, Elleder M, Vulpe CD (2007) Proteomic analysis of hepatic iron overload in mice suggests dysregulation of urea cycle, impairment of fatty acid oxidation, and changes in the methylation cycle. Am J Physiol Gastrointest Liver Physiol 292:G1490–G1498

Pulliam JF, Jennings CD, Kryscio RJ, Davis DG, Wilson D, Montine TJ, Schmitt FA, Markesbery WR (2003) Association of HFE mutations with neurodegeneration and oxidative stress in Alzheimer's disease and correlation with APOE. Am J Med Genet B Neuropsychiatr Genet 119B: 48–53

Restagno G, Lombardo F, Ghiglione P, Calvo A, Cocco E, Sbaiz L, Mutani R, Chio A (2007) HFE H63D polymorphism is increased in patients with amyotrophic lateral sclerosis of Italian origin. J Neurol Neurosurg Psychiatry 78:327

Ristic S, Lovrecic L, Brajenovic-Milic B, Starcevic-Cizmarevic N, Jazbec SS, Sepcic J, Kapovic M, Peterlin B (2005) Mutations in the hemochromatosis gene (HFE) and multiple sclerosis. Neurosci Lett 383:301–304

Ron D, Walter P (2007) Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol 8:519–529

Rutkowski DT, Kaufman RJ (2007) That which does not kill me makes me stronger: adapting to chronic ER stress. Trends Biochem Sci 32:469–476

Rutkowski DT, Arnold SM, Miller CN, Wu J, Li J, Gunnison KM, Mori K, Sadighi Akha AA, Raden D, Kaufman RJ (2006) Adaptation to ER stress is mediated by differential stabilities of pro-survival and pro-apoptotic mRNAs and proteins. PLoS Biol 4:e374

Sado M, Yamasaki Y, Iwanaga T, Onaka Y, Ibuki T, Nishihara S, Mizuguchi H, Momota H, Kishibuchi R, Hashimoto T et al (2009) Protective effect against Parkinson's disease-related insults through the activation of XBP1. Brain Res 1257:16–24

Salvador GA (2010) Iron in neuronal function and dysfunction. BioFactors 36:103–110

Salvador GA, Oteiza PI (2010) Iron overload triggers redox-sensitive signals in human IMR-32 neuroblastoma cells. Neurotoxicology 32:75–82

Saxena S, Caroni P (2011) Selective neuronal vulnerability in neurodegenerative diseases: from stressor thresholds to degeneration. Neuron 71:35–48

Saxena S, Cabuy E, Caroni P (2009) A role for motoneuron subtype-selective ER stress in disease manifestations of FALS mice. Nat Neurosci 12:627–636

Schröder M (2007) Endoplasmic reticulum stress responses. Cell Mol Life Sci 65:862–894

Shinkai Y, Yamamoto C, Kaji T (2011) Lead induces the expression of endoplasmic reticulum chaperones GRP78 and GRP94 in vascular endothelial cells via the JNK-AP-1 pathway. Toxicol Sci 114:378–386

Sutedja NA, Sinke RJ, Van Vught PW, Van der Linden MW, Wokke JH, Van Duijn CM, Njajou OT, Van der Schouw YT, Veldink JH, Van den Berg LH (2007) The association between H63D mutations in HFE and amyotrophic lateral sclerosis in a Dutch population. Arch Neurol 64:63–67

Sutedja NA, Fischer K, Veldink JH, van der Heijden GJ, Kromhout H, Heederik D, Huisman MH, Wokke JJ, van den Berg LH (2009) What we truly know about occupation as a risk factor for ALS: a critical and systematic review. Amyotroph Lateral Scler 10:295–301

Tabas I, Ron D (2011) Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. Nat Cell Biol 13:184–190

Tomatsu S, Orii KO, Fleming RE, Holden CC, Waheed A, Britton RS, Gutierrez MA, Velez-Castrillon S, Bacon BR, Sly WS (2003) Contribution of the H63D mutation in HFE to murine hereditary hemochromatosis. Proc Natl Acad Sci USA 100:15788–15793

Urano F, Wang X, Bertolotti A, Zhang Y, Chung P, Harding HP, Ron D (2000) Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. Science 287:664–666

Vecchi C, Montosi G, Zhang K, Lamberti I, Duncan SA, Kaufman RJ, Pietrangelo A (2009) ER stress controls iron metabolism through induction of hepcidin. Science 325: 877–880

Ventura JJ, Hubner A, Zhang C, Flavell RA, Shokat KM, Davis RJ (2006) Chemical genetic analysis of the time course of signal transduction by JNK. Mol Cell 21:701–710

Waheed A, Parkkila S, Zhou XY, Tomatsu S, Tsuchihashi Z, Feder JN, Schatzman RC, Britton RS, Bacon BR, Sly WS (1997) Hereditary hemochromatosis: effects of C282Y and H63D mutations on association with beta2-microglobulin, intracellular processing, and cell surface expression of the HFE protein in COS-7 cells. Proc Natl Acad Sci USA 94:12384–12389

Wang XS, Lee S, Simmons Z, Boyer P, Scott K, Liu W, Connor J (2004) Increased incidence of the Hfe mutation in amyotrophic lateral sclerosis and related cellular consequences. J Neurol Sci 227:27–33

Xia Z, Dickens M, Raingeaud J, Davis RJ, Greenberg ME (1995) Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis. Science 270:1326–1331

Yang Y, Hentati A, Deng HX, Dabbagh O, Sasaki T, Hirano M, Hung WY, Ouahchi K, Yan J, Azim AC et al (2001) The gene encoding alsin, a protein with three guanine-nucleotide exchange factor domains, is mutated in a form of recessive amyotrophic lateral sclerosis. Nat Genet 29: 160–165

Ye Z, Connor JR (2000) Identification of iron responsive genes by screening cDNA libraries from suppression subtractive hybridization with antisense probes from three iron conditions. Nucleic Acids Res 28:1802–1807

Ye J, Rawson RB, Komuro R, Chen X, Dave UP, Prywes R, Brown MS, Goldstein JL (2000) ER stress induces cleavage of membrane-bound ATF6 by the same proteases that process SREBPs. Mol Cell 6:1355–1364

Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K (2001) XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. Cell 107:881–891

You KR, Liu MJ, Han XJ, Lee ZW, Kim DG (2003) Transcriptional regulation of the human transferrin gene by GADD153 in hepatoma cells. Hepatology 38:745–755

Zecca L, Youdim MB, Riederer P, Connor JR, Crichton RR (2004) Iron, brain ageing and neurodegenerative disorders. Nat Rev Neurosci 5:863–873