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Myelin Under Stress

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Abstract

The capacity to fold proteins properly is fundamental for cell survival. Secreted and transmembrane proteins are synthesized in the endoplasmic reticulum (ER), an organelle that has the ability to discriminate between native and non-native proteins, in a process called protein quality control. When folding is not properly achieved, misfolded proteins can accumulate. The terminally misfolded proteins are typically retro-translocated into the cytoplasm for degradation by the proteasome, in a process known as endoplasmic reticulum associated degradation. However, if the degradation is insufficient, accumulation of abnormal proteins in the ER activates the unfolded protein response (UPR), a complex set of new signals aimed to further reduce the load of abnormal protein in the ER. Massive synthesis of myelin lipids and proteins is necessary to support myelinogenesis. Not surprisingly, therefore, ER stress (including the UPR), the proteasome and autophagy (lysosomes), have been implicated in myelin disorders, such as Pelizaeus-Merzbacher disease and vanishing white matter disease in the central nervous system and Charcot-Marie-Tooth neuropathies in the peripheral nervous system. Here we will discuss recent evidence supporting an important role for ER stress in myelin disorders.

Keywords

ER stress; unfolded protein response; myelin; Schwann cell; oligodendrocyte

Introduction

The ER is a highly specialized organelle, continuous with the nuclear membrane. Proteins destined for secretion or insertion into the cell membranes, are synthesized on ER-bound ribosomes and cotranslationally translocated into the ER (Anelli and Sitia 2008; Gilmore and Blobel 1985; Kleizen and Braakman 2004). In addition to the optimal redox conditions, the ER also provides resident chaperones and folding enzymes that exhibit different biochemical properties, necessary for correct protein folding, oligomerization and post-translational modifications (Schroder and Kaufman 2005; Zhang and Kaufman 2006). For example, some chaperones such as BiP (GRP78), do not actively catalyze protein folding, but rather keep proteins in a folding-competent state while preventing aggregation (Bertolotti et al. 2000); others such as calnexin (CNX) and calreticulin (CRT) recognize and assist the folding of nascent chains of N-glycosylated proteins. Finally, enzymes such as disulfide isomerase (PDI) catalyze protein-folding reactions accelerating the rate of correct disulfide bond formation (Kaufman 1999). Proteins that fail to fold are eventually retrotranslocated across the ER membrane for proteasomal degradation.

ER homeostasis is vital for cell function and survival. Alterations in calcium storage or in the redox status, sugar/glucose deprivation or the expression of misfolded proteins,

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compromise the folding capacity of the ER, resulting in the accumulation of unfolded proteins in the *lumen*. An imbalance between the unfolded protein load and the ability to process that load causes ER stress. To maintain homeostasis, the mammalian ER has evolved molecular transducers that sense the stress in the *lumen* and signal to the cytoplasm and the nucleus, triggering a series of responses collectively termed unfolded protein respose (UPR) (Harding et al. 2002; Ron and Walter 2007; Rutkowski et al. 2006).

The mammalian UPR exhibits an integrated signaling network of three ER transmembrane sensors: pancreatic ER kinase (PERK), inositol requiring kinase 1 (IRE1), and activating transcription factor 6 (ATF6). These factors coordinate the cell response to ER stress via transcriptional and translational control (Harding et al. 2002; Kaufman 1999; Mori et al. 2000). PERK phosphorylates eIF2alpha to attenuate translation (Harding et al. 2000). Paradoxically, eIF2alpha phosphorylation enhances the translation of some proteins, including the transcription factor ATF4, which in turn induces genes involved in amino acid metabolism, protein secretion and in the anti-oxidant response (Rutkowski and Kaufman 2003). Notably, eIF2alpha can also be phosphorylated by other kinases such as PKR and GCN2, independently of ER stress. For this reason this arm of the UPR is called integrated stress response (ISR) (Ron and Walter 2007).

Slightly after translational repression, IRE1 and ATF6 activate the transcription of genes encoding components that increase ER folding capacity, protein export, and degradation. In particular, IRE1 has an endoribonuclease activity that elicits the unconventional splicing of the mRNA for the transcription factor Xbp-1. The spliced form, sXbp-1, encodes a potent transcription factor that activates UPR target genes that promote endoplasmic reticulum associated degradation (ERAD) and ER biogenesis (Acosta-Alvear et al. 2007).

ATF6 is instead translocated to the Golgi were it is proteolytically cleaved by the site-1 and site-2 proteases (SP1 and SP2). This cleavage generates a ~60 kDa bZip-containing fragment that migrates to the nucleus were it activates the transcription of chaperones (such as BiP) and ERAD proteins (Wu et al. 2007; Yamamoto et al. 2007).

However, if the cell cannot cope with the unfolded protein overload, these transducers induce programmed cell death. At present, three main apoptotic pathways, emanating from the UPR have been identified:the IRE1/c-Jun-N-terminal protein kinase (JNK) pathway, the caspase-12 pathway and the PERK/CHOP pathway. Still, what determines the balance between anti- versus pro-apoptotic signals, remains a crucial question (Rutkowski and Kaufman 2007).

The intensity and the duration of the UPR appear to be important to determine cell fate. In fact, recent work has indicated that survival is favored during mild stress, a condition in which pro-apoptotic mRNAs and proteins are intrinsically less stable compared to those that promote adaptation (Rutkowski et al. 2006). Moreover, in human cells, during persistent ER stress, the IRE1 and ATF-6 arms of the UPR are attenuated while the PERK/CHOP arm appears to be maintained. Artificially prolonged IRE1 activity promotes cell survival, indicating a possible link between this arm of the UPR and cell surivival (Lin et al. 2007). These observations may also provide a basis for context-dependent cell death; different cells may activate the three arms of the UPR differently, or be able to maintain all of the arms of the UPR active for longer, favoring survival.

Myelinogenesis requires massive cellular synthesis of myelin lipids and proteins. Not surprisingly, therefore, ER stress (including UPR and ISR), autophagy and proteasome inefficiency, have been implicated in myelin disorders in both the central nervous system (CNS) and the peripheral nervous system (PNS) (Figure 1). For example, UPR and ISR activation was recently associated with central myelin damage in mouse models of Pelizaeus

Merzbacher disease (PMD), attributable to mutations of proteolipid protein, or in mice with enforced expression of interferon-γ in the CNS, respectively. Genetic modulation of the UPR or ISR altered the severity of the disease in each of these mouse models (Lin et al. 2005;Southwood et al. 2002). Moreover, various mutations in subunits of eukaryotic translation factor EIF2B (its substrate, EIF2α, is an important component of ER stress response), produce vanishing white matter disease (VWM) (Proud 2001;van der Knaap et al. 2006).

In the PNS some mutant P0 and PMP22 proteins, causing Charcot-Marie-Tooth type 1B (CMT1B) and CMT1A disease in humans, respectively, may be retained in the ER. Whereas P0 mutant elicits a pathogenetic UPR that can be genetically modulated (Pennuto et al. 2008; Wrabetz et al. 2006), PMP22 mutants are retrotranslocated for degradation, then aggregate and lead to inefficient proteasome function, toxic to the cell (Fortun et al. 2005; Notterpek et al. 1999).

PLP and Pelizaeus-Merzbacher disease

Proteolipid protein (PLP) is the major myelin protein in the CNS (Griffiths et al. 1998; Hudson 2004). The PLP gene is composed of 7 exons and encodes for two tetraspan proteins, PLP and its smaller isoform DM20, generated from alternative splicing of exon 3B (Vouyiouklis et al. 2000). Various mutations in the X-linked gene for PLP1 give rise to Pelizeaus-Merzbacher disease (PMD) and spastic paraplegia type II (SPG2) in humans (Hudson et al. 2004). PMD is a neurodegenerative disorder characterized by diffuse hypomyelination in the CNS, and the phenotype can vary from mild to extremely severe, depending on the mutation. The most severe cases of PMD are due to either duplication of the PLP locus, or to point mutations that can act through a gain of function (Hudson et al. 2004).

Several natural and transgenic mouse models are currently available to study PLP function and the pathogenesis of PMD. Notably, some mutations found in patients are also naturally occurring in mice. For example, the A242V amino acid substitution that causes a severe form of PMD in humans, is found in the myelin synthesis-deficient mouse (*msd*), whereas the I186T mutation, that in humans results in a milder disease, is found in the rumpshacker (*rsh*) mouse (Gow et al. 1994b; Nave and Griffiths 2004). The molecular mechanisms underlying the diverse phenotypes are poorly understood.

Accumulating data show that in the majority of the severe forms of PMD due to point mutations, the PLP/DM20 protein is localized abnormally in the ER rather then being transported to the forming myelin membrane, suggesting that the altered trafficking of the protein is involved in the pathogenesis of the disease (Gow et al. 1994a; Gow and Lazzarini 1996). In some cases, the misfolding of the mutant protein leads to exposure of unpaired cysteine residues that engage in intramolecular crosslinks and may cause ER retention (Dhaunchak and Nave 2007). ER retention is associated with up-regulation of the mRNA for BiP and other molecular chaperones in several PLP-mutant animals including msd and rsh mice (Gow et al. 1998; Hudson and Nadon 1992; Southwood and Gow 2001). These observations led to the analysis of the role of the UPR in PLP-mutant mice. In *msd*, *rsh* and jimpy (*jp*) mice, the mutant PLP protein triggered the up-regulation of chaperones such as BiP and Erp72 and of the transcription factors CHOP and ATF3, suggesting the activation of an UPR (Gow 2004; Southwood et al. 2002). This indicates a similarity in the molecular pathogenesis of the disease in the three models, despite the different mutations and disease severity. Strikingly, genetic removal of *CHOP* worsened the disease phenotype dramatically in *rsh* (Southwood et al. 2002). While *rsh* mice have a normal life-span, *rsh*/Chop null mice die as early as 5 weeks of age, and exhibit frequent seizures following handling or sudden

noises. This extreme exacerbation of the phenotype is accompanied by an increase in oligodendrocyte apoptosis in the spinal cord and in the optic nerve, from 3-fold in *rsh* to 5-fold in *rsh*/Chop null, when compared to wt (Sharma and Gow 2007; Southwood et al. 2002). However, whether this mild increase in cell death is enough to explain the dramatic worsening of the phenotype is not clear. Still, these data indicate that the UPR can modulate the disease severity but that CHOP has a protective role in oligodendrocytes.

These observations raise an important issue related to the role of CHOP during the UPR. While CHOP is pro-apoptotic in various cell types in vitro and in vivo (Marciniak et al. 2004; Oyadomari et al. 2002a; Zinszner et al. 1998), it appears to be protective in oligodendrocytes. One explanation for this discrepancy could be genetic background. In fact, whereas *rsh* mice with a C3H background have a normal lifespan, with a C57BL/6 background they die at around postnatal day 30 (Al-Saktawi et al. 2003).The reason for this difference is still unknown, but could reflect an alteration in the activation of CHOP relative to other UPR mediators such as XBP-1 (McLaughlin et al. 2007), or the influence of modifying genes. The *rsh*/Chop null mice analyzed in the work from Southwood and colleagues were on a mixed C3H-C57BL/6 background raising the possibility that the worsening in the phenotype in the absence of *Chop* was due to the presence of C57BL/6 background, rather than to a protective role of CHOP. However, *rsh*//Chop+/+ mice regenerated from the siblings of experimental animals, maintained a mild phenotype even in the continued presence of C57BL/6 background, making the background hypothesis unlikely (Southwood et al. 2002). Another possibility could be cell specificity. It is possible that the target genes of CHOP vary from cell to cell, and in agreement with this, downstream-of-CHOP (Doc) genes (Wang et al. 1998) are not induced in PMD models, suggesting that the targets of CHOP in oligodendrocytes could be different from those in other cell types.

Interestingly, ablation of the transcription factor ATF3 or of caspase-12, both supposed to have pro-apoptotic functions in the UPR, has at best only a marginal effect on the disease severity in *msd* and *rsh* mice (Sharma and Gow 2007; Sharma et al. 2007), indicating that these genes are not related to cell survival in PLP mutants. Finally, no UPR could be identified in *md* rat brain, despite oligodendrocyte death and short lifespan (Hudson and Nadon 1992). Further studies will be required to understand the relationship between specific mutations, UPR, oligodendrocyte death and overall phenotype in PLP mutant animals.

Vanishing white matter disease

Leukoencephalopathy with vanishing white matter (VWM) is an autosomal recessive disease clinically characterized by progressive ataxia, spasticity and seizures (van der Knaap et al. 2006). VWM mainly affects the oligodendrocytes in the brain, often described as "foamy" in appearance, with abundant cytoplasm and abnormal mitochondria. In the most severe cases there is diffuse oligodendrocyte death by apoptosis. Astrocytes can also appear abnormal in morphology and in their differentiation (Scheper et al. 2006). The primary defect of VWM resides in mutations in any of the five subunits of the translation initiation factor eIF2B (Leegwater et al. 2001; Richardson et al. 2004; van der Knaap et al. 2002). The initiation of protein synthesis is a complex process that requires the interplay between mRNAs, tRNAs, ribosomes and various eukaryotic initiation factors (eIFs) (Pestova et al. 2001). The eIF2-GTP complex is necessary to deliver the initiator methionyl-tRNA (Met-tRNAi) to the ribosome when the proper AUG sequence is identified. This is followed by the hydrolysis of the GTP to GDP with consequent release of eIF2. The guanine nucleotide exchange factor (GEF) eIF2B catalyzes the exchange of GDP to GTP on eIF2, to enable its association to another Met-tRNAi and recruitment to the ribosomal pre-initiation complex (Scheper et al. 2006). The eIf2 factor comprises three subunits, α, β and γ. As previously

mentioned, phosphorylation of eIF2α is involved in translational control during the UPR. The phosphorylated eIF2α converts eIF2 from a substrate of eIF2B to a strong competitor, thus reducing the formation of the eIF2-GTP complex and therefore inhibiting protein synthesis. Mutations in eIF2B reduce its activity, and VWM patients have residual eIF2B activity ranging from 30–80%, with a correlation between the reduction of eIF2B activity and age of unset and severity of the disease (Fogli et al. 2004).

One of the peculiar features of VWM disease is sensitivity to stress. Fever, acute fright or head trauma can lead to rapid neurological deterioration (van der Knaap et al. 2006). This observation, coupled with the interplay of eIF2B and eIF2α, had prompted the investigation of the role of the UPR in VWM. Analysis of brain tissue from VWM patients indicated that all three branches of the UPR are activated (van der Voorn et al. 2005; van Kollenburg et al. 2006b). This activation is exclusively in white matter and predominantly in oligodendrocytes and astrocytes. How does the activation of the UPR result from the reduced activity of eIF2B? One possibility is that mutations in eIF2B alter the global protein synthesis rate. Surprisingly, in lymphoblasts from VWM patients no differences in the regulation of protein synthesis were found (van Kollenburg et al. 2006a). However there was a slight increase in ATF4 expression (Li et al. 2004).This in turn was associated with an increase in CHOP levels that in some circumstances could further sensitize the cells to ER-stress (McCullough et al. 2001), predisposing the cells to apoptosis. Another possibility is that UPR activation occurs normally during life, for example in the case of fever, and that mutations in eIF2B impair the adaptive response of such UPR.

But if eIF2 is such a vital component of protein synthesis in all cell types, why are only glial cells in the CNS affected? Oligodendrocytes need to synthesize vast amount of proteins and lipids necessary for the formation of the myelin sheath, which may render them more sensitive to ER homeostasis alterations. Currently, there are no animal models to study VWM, but they appear necessary to properly understand the pathophysiology of this complex disease.

Interferon-γ in the CNS. ER stress modulates the response of the oligodendrocytes to interferon

Interferon-γ is a pro-inflammatory cytokine secreted by activated T-lymphocytes. While not normally present in the CNS, it plays complex roles in immune-mediated demyelinating disorders, such as multiple sclerosis (MS) in humans and experimental autoimmune encephalomyelitis (EAE) in animals (Popko et al. 1997). For example, treatment of MS patients with interferon-γ exacerbates the disease (Panitch 1992; Panitch et al. 1987), and transgenic mice expressing this cytokine in the CNS display some myelin abnormalities (Corbin et al. 1996), whereas low levels of ectopically expressed interferon-γ appear to protect mouse CNS from cuprizone (a copper chelator) induced demyelination (Gao et al. 2000). In vitro, differentiating oligodendrocytes undergo death by apoptosis after treatment with interferon-γ (Baerwald and Popko 1998). This process is accompanied by the up-regulation of some ER-stress markers, such as BiP, CHOP, caspase-12 and phosphorylated eIF2α (Lin et al. 2005). Similarly, these ER-stress markers correlated with hypomyelination and oligodendrocyte loss in a mouse model in which interferon-γ was ectopically expressed by astrocytes in the CNS from embryonic day 14 (Lin et al. 2005). When these mice were crossed into a PERK +/− background, the phenotype worsened dramatically, indicating that the stress response activated through the PERK pathway could have a protective role in immune mediated hypomyelinating disorders (Lin et al. 2005). This is further supported by the observation that, after cuprizone treatment, PERK +/− mice displayed a significantly reduced number of remyelinated axons, suggesting that the ER-stress also modulates the response of remyelinating oligodendrocytes to interferon-γ (Lin et al. 2006).

Why does interferon-γ activate a stress response in oligodendrocytes? It has been shown that this cytokine increases the expression of MHC class I molecules, and that accumulation of these molecules in oligodendrocytes causes hypomyelination accompanied by tremors and seizures (Baerwald et al. 2000). Developing and remyelinating oligodendrocytes are already synthesizing huge amounts of proteins and could develop a physiological UPR, similar to that observed in plasma cells and pancreatic β-cells (Kaufman 1999). This would make them more sensitive to the accumulation of MHC class I molecules, and more prone to ER stress. Accordingly, mature oligodendrocytes, that are synthesizing only low, steady state levels of myelin proteins, are much less sensitive to the detrimental effects of interferon-γ (Lin et al. 2005; Lin et al. 2006).

PMP22 overexpression and point mutations in the PNS

PMP22 (peripheral myelin protein 22) is a 22 kD glycoprotein that is a minor component of the myelin sheath of peripheral nerve, mainly localized to compact myelin (Snipes et al. 1992; Suter 2004). Most of the knowledge about the role of PMP22 in peripheral nerve comes from genetics, since PMP22 is the most common cause of neuropathies in humans and rodents. In humans, duplications of a chromosomal region containing the PMP22 gene account for most cases of CMT1A, although point mutations also exist (Snipes et al. 1999; Suter 2004). Some mutations described in human families are also naturally occurring in mice, such as the G150D (DSS in humans) and the L16P (CMT1 in humans) found in trembler (*Tr*) and *Tr-j* mice respectively (Suter 2004). The trafficking of the *Tr* and *Tr-j* mutant protein is different from that of wt PMP22, with *Tr*-PMP22 mainly retained in the ER (Colby et al. 2000; Naef et al. 1997), and *Tr-j*-PMP22 retained in the intermediate compartment between the ER and the Golgi (Tobler et al. 1999). Interestingly, the ER-retained *Tr*-PMP22 associates with the chaperone calnexin, but not with BiP, with the consequence that the UPR is not activated in these mutants (Dickson et al. 2002).

One of the characteristics of PMP22 is its rapid turnover, with the majority of the newly synthesized protein rapidly degraded via the proteasome (Notterpek et al. 1999; Pareek et al. 1997). Overexpressed and mutated PMP22 accumulate in aggregates in the cytoplasm, and this correlates with a reduced activity of the ubiquitin-proteasome system (Fortun et al. 2005; Notterpek et al. 1999; Ryan et al. 2002). These protein aggregates are termed aggresomes (Johnston et al. 1998). Aggresomes are membrane free cellular inclusions, rich in ubiquitinated proteins, usually localized near the centrosome, an area enriched in proteasomal subunits and heat shock proteins (HSPs) (Kopito 2000). Accordingly, PMP22 in aggresomes appears to be ubiquitinated, and associates with proteasomal components and with molecular chaperones such as HSP-70 (Fortun et al. 2005; Notterpek et al. 1999). Whether the formation of aggresomes is harmful or protective in various disease paradigms is still a matter of debate, but accumulating data point towards a protective role at least in PMP22 disease models. For example, cell transfections with a series of three PMP22 mutant proteins has shown that the larger aggregates correlate with the less severe phenotypes (Isaacs et al. 2002). Moreover, if the aggregates were toxic, cell death could be the expected outcome of the toxicity, while very little cell death is observed in PMP22-associated neuropathies (Sancho et al. 2001).

The accumulation of PMP22 in aggresomes results instead in a concomitant activation of autophagy (Fortun et al. 2003). Autophagy is defined as the process by which a portion of cytosol or organelle is sequestered in a double membrane structure called autophagosome, which then fuses with lysosomes (Ohsumi 2001). PMP22 aggreagates are indeed surrounded by autophagosomes and lysosomes, which appear to be involved in the clearance of the aggresomes (Fortun et al. 2003). Stimulation of autophagy hinders the accumulation of proteasome substrates and correlates with a reduction in the formation of the aggresomes

(Fortun et al. 2007). In parallel to autophagy, an increase in the expression of molecular chaperones aids the cell in disposing of misfolded proteins (Fortun et al. 2007). These studies support a model in which the proteasome is inefficient, misfolded proteins aggregate in the cytoplasm and are degraded via the autophagic-lysosomal pathway, further aided by cytoplasmic chaperones. These observations suggest that the development of pharmacological agents to stimulate these pathways would be a promising therapeutic approach to eliminate protein aggregates at least in PMP22-related CMT neuropathies (Rangaraju et al. 2008).

P0S63del and UPR modulation in Schwann cells

We might have thought that the main problem with PMP22 was the lack of adaptive UPR; instead myelin protein zero (*MPZ*, P0) mutants elicit a UPR, and this also causes myelin abnormalities (Table 1). P0 is the major protein in peripheral nerve myelin, where it accounts for up to 50% of the total protein (Kirschner et al. 2004). Analysis of homozygous and heterozygous *Mpz*-null mice has shown that P0 is required in myelin compaction during development and for long-term maintenance of the myelin sheath (Giese et al. 1992). In humans, diverse mutations in P0 cause a range of hereditary neuropathies, suggesting diverse gain of function mechanisms (Wrabetz et al. 2004). For example, deletion (S63del) or conversion of serine 63 to cysteine (S63C) results in CMT1B or Dèjèrine-Sòttas syndrome, respectively. Consistent with toxic gain of function, when expressed in mouse together with wild type P0, the mutant P0s produce a demyelinating or hypomyelinating neuropathy that mimics the corresponding human disease. In particular, S63del never reaches the myelin sheath and is instead retained in the ER (Wrabetz et al. 2006).

Accumulation of S63del in the ER triggers a canonical UPR indicating a toxic gain of function (Pennuto et al. 2008; Wrabetz et al. 2006). Notably, in contrast to what happens in the CNS of PLP mutants (Southwood et al. 2002), in S63del mice the genetic ablation of the transcription factor CHOP ameliorates the demyelinating phenotype and completely rescues the motor deficit indicating that the UPR is pathogenetic (Pennuto et al. 2008). How does this UPR produce demyelination and why does the removal of CHOP improve the phenotype? One possibility is that CHOP induction activates Schwann cell apoptosis and therefore, demyelination. However the level of cell death in S63del mice is very low when compared to a number of misfolded protein disorders with primary cell death, including diabetes (Oyadomari et al. 2002b), GM1-gangliosidosis (Tessitore et al. 2004) and Pelizeaus-Merzbacher disease (Southwood et al. 2002). Accordingly, S63del nerves do not show an obvious reduction in numbers of Schwann cells, or a phenotype typical of extensive Schwann cell death (Messing et al. 1992). Moreover, the rise in apoptosis in S63del mice is delayed by weeks relative to CHOP induction and parallels better the rise in demyelinated fibers (Pennuto et al. 2008). Finally, CHOP is usually detected in nonpyknotic Schwann cell nuclei, associated with normal myelin sheaths (Pennuto et al. 2008), suggesting that UPR and CHOP induce demyelination with limited secondary Schwann cell death and not vice-versa. In fact, other demyelinating neuropathies not associated with UPR manifest similar low levels of apoptosis (Sancho et al. 2001). This provides further support for the idea that CHOP induction in the context of UPR does not necessarily imply cell death (Rutkowski et al. 2006).

Another appealing hypothesis is that CHOP could perturb myelin stoichiometry, either transcriptionally or at the translational level–GADD34, a target gene of CHOP, regulates the dephosphorylation of eIF2α and thereby stress-induced changes in translation of specific mRNAs (Marciniak et al. 2004). As we have seen in the case of VWM, subtle changes in translational control may exert dramatic effects on myelin homeostasis in the CNS, and this is likely to be also true in the PNS. Finally, the reason why CHOP appears to have a

maladaptive role in Schwann cells as opposed to the protective role in oligodendrocytes (Southwood et al. 2002) remains unclear. A comparison of CHOP target genes, as well as the relative level of activation of the arms of the UPR, in the two pathological cells, could illuminate the differing response (Figure 2).

Conclusion and remarks

ER stress has been implicated in various diseases, ranging from cancer to diabetes (Zhao and Ackerman, 2006). Glial cells also appear to be vulnerable to ER stress, and the UPR, or alterations to some of its mediators, can perturb myelination by both oligodendrocytes and Schwann cells. This susceptibility may have various causes. Myelination is a complex process that requires a precise stoichiometry in gene dosage and in protein and lipid synthesis. It is possible that induction of the UPR alters this tightly controlled mechanism, with detrimental effects. The UPR in fact attenuates translation, broadly alters the transcription and stability of specific mRNAs (Hollien and Weissman 2006), and has global effects on the dosage, folding and function of other metastable proteins (Gidalevitz et al. 2006). For example, in the PNS, PMP22 could be considered a metastable protein, with much of the newly synthesized PMP22 rapidly degraded under physiological conditions (Pareek et al. 1997). In this context, it is worth noting that alteration of the dosage of PMP22 causes CMT1A, the most common hereditary demyelinating neuropathy.

Another possibility is that some of the mechanisms activated during the UPR may overlap with those necessary for myelin membrane production, creating a sort of competition. For example, Xbp-1 increases the expression of genes related to phospholipid biosynthesis and ER membrane expansion (Acosta-Alvear et al. 2007; Sriburi et al. 2004), and ATF6 is cleaved in the Golgi by the SP-1 and SP-2 proteases, that are also responsible for the cleavage and activation of the sterol regulatory element binding protein 1 and 2 (SREBPs), which are involved in the expression of cholesterol/lipid biosynthesis genes during myelination (Leblanc et al. 2005; Verheijen et al. 2003).

The mouse models reviewed here also indicate that the effects of the UPR *in vivo* are not easily predicted. The cell context appears to be important to determine if the response will be adaptive or maladaptive. For example the CHOP arm of the UPR is adaptive in oligodendrocytes of *rsh* mice (Southwood et al. 2002) and maladaptive in Schwann cells of P0 S63del mice (Pennuto et al. 2008). Notably, the maladaptive effect of CHOP in S63del Schwann cells results primarily in hypomyelination and demyelination and not in cell death, suggesting that the cell context may be also important to determine what form the maladaptive response takes.

Finally, these observations raise a corollary point: most of the studies on ER stress and UPR have been conducted in cell cultures with pharmacological induction of ER stress. However these studies have not always predicted the range of effects in stressed cells *in vivo*, where different mechanisms cause ER stress. Further studies will define the range of response to ER stress *in vivo*.

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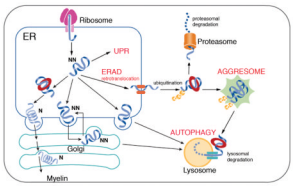

Figure 1. The possible outcomes of protein misfolding in the endoplasmic reticulum (ER) of glial cells

In the endoplasmic reticulum non-native proteins are assisted in their folding by various chaperones. If the native conformation is correctly achieved, the protein transits through the Golgi and reaches the myelin sheath. Terminally misfolded (or non-native) proteins are usually retrotranslocated for ER associated degradation (ERAD) by the proteasome. If the degradative machinery is unable to prevent the accumulation of misfolded protein in the ER, an unfolded protein response (UPR) can be elicited. In some circumstances, misfolded proteins are retrotranslocated but accumulate in the cytoplasm forming the so called aggresomes. This accumulation can in turn lead to the activation of autophagy and lysosomal degradation. N, native; NN, non-native. Modified with permission from (Yerbury et al. 2005)

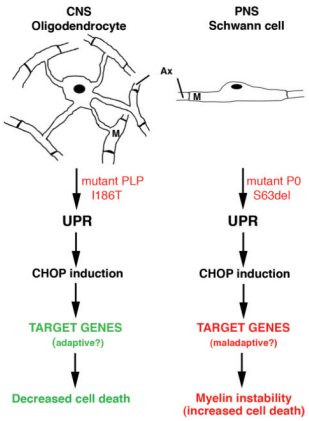

Figure 2. The transcription factor CHOP has different roles in oligodendrocytes and in Schwann cells

Accumulation of misfolded PLP and P0 proteins triggers an unfolded protein response (UPR) in oligodendrocytes and Schwann cells, respectively. However, while the genetic ablation of *CHOP* exacerbates the phenotype in the CNS, it improves it in the PNS. This suggests that the target genes of CHOP could be different in the two cell types, and that they have an adaptive role in oligodendrocytes and a maladaptive one in Schwann cells. Ax, axon; M, myelin.