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CHOP and the endoplasmic reticulum stress response in myelinating glia

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Abstract

The unfolded protein response (UPR) comprises kinase signaling and transcription factor activation cascades delineated over the past 20 years. Most studies conclude that this stress response is adaptive but, nevertheless, includes maladaptive programs involving CHOP expression which drive cell-autonomous apoptosis. Herein, we highlight several studies of UPR diseases involving myelinating glia of the central and peripheral nervous systems that do not support a primary role for CHOP in apoptosis. In oligodendrocytes, CHOP expression apparently protects against death whereas in Schwann cells, CHOP promotes demyelination in the absence of cell death. Together, these studies demonstrate that CHOP should be viewed more broadly as a cell- and context-specific mediator of adaptive or maladaptive responses to stress rather than a proapoptotic transcription factor.

Keywords

Charcot-Marie-Tooth disease; CNS; disease mechanisms; gain of function diseases; multiple sclerosis; oligodendrocyte; neurodegeneration; Pelizaeus-Merzbacher disease; PNS; Schwann cells; spastic paraplegia; vanishing white matter

Genetic analyses of the UPR (see Glossary) have established this metabolic stress response as a set of signaling cascades that integrate molecular chaperone induction with endoplasmic reticulum-associated protein degradation (ERAD) and transient suppression of global translation [reviewed by ^{1,2}]. Together, these cascades and proteolytic processing of membrane-tethered transcription factors [e.g. activator of transcription factor 6, (ATF6)] integrate the response and serve as negative feedback loops to ameliorate stress stemming from perturbed protein trafficking in the secretory pathway.

UPR-mediated suppression of global translation has been studied in detail in mammals, in many cell types, in vitro and in vivo. In its simplest incarnation, this negative-feedback loop is initiated by activation of pancreatic ER kinase (PERK), which phosphorylates eukaryotic initiation factor 2 α (eIF2 α). Phospho-eIF2 α (eIF2 α P) reduces GTP exchange on eIF2 and suppresses assembly of the pre-initiation complex [³]. Nevertheless, translation of specific mRNAs is stimulated under these conditions, including *ATF4*, CCAAT-enhancer-binding protein homologous protein (*CHOP*) and growth-arrest and DNA damage protein 34 (*GADD34*). The encoded proteins undoubtedly carry out myriad functions that are poorly characterized, but they eventually effect the dephosphorylation of eIF2 α , and translation resumes.

The CHOP transcription factor features prominently in PERK pathway signaling, particularly as a marker of the UPR. While widely touted as a proapoptotic protein, both in vitro and in vivo, contemporary studies demonstrate that such a narrow view is untenable [4–6]. Rather, CHOP serves context- and cell-type specific roles in several diseases that may be more appropriately defined as adaptive or maladaptive responses to metabolic stress.

Attention has recently focused on the characterization of diseases arising from UPR activation, including neurodegenerative disorders such as Alzheimer, Parkinson, amyotrophic lateral sclerosis and multiple sclerosis as well as non-neural diseases such as metabolic syndrome [2,7]. Herein, we highlight degenerative diseases of the central nervous system (CNS) and peripheral nervous system (PNS) involving myelinating glia. These cells provide interesting case studies because they synthesize large amounts of lipids and proteins, some of which are metastable with high rates of misfolding. Not surprisingly, coding region mutations exacerbate endoplasmic reticulum (ER) stress, induce the UPR and cause diseases which encapsulate aspects of the context- or cell type-dependent behavior of CHOP and the UPR.

CNS myelination and oligodendrocyte pathology

The UPR is implicated in at least four diseases involving oligodendrocytes: Pelizaeus-Merzbacher disease (PMD), spastic paraplegia type II (SPG2), multiple sclerosis (MS) and vanishing white matter disease (VWM). Likely PERK pathway signaling in oligodendrocytes (Figure 1), is overlaid onto adaptive (green) and maladaptive (red) processes inferred by experimental data from animal models of PMD, SPG2 and MS [4,5]. In the case of VWM, the pathophysiology appears complex and currently lacks sufficient clarity for analysis. Below, we highlight salient aspects of UPR activation in these diseases.

PMD and SPG2

Proteolipid protein 1 (PLP1) is a structural protein [8] comprising 50% of the protein in CNS myelin. Three genetic lesions in the X-linked *PLP1* gene – deletions, duplications and coding region mutations – account for most patients and cause disease by distinct mechanisms [reviewed by 9]. Many coding region mutations disrupt PLP1 trafficking in differentiated oligodendrocytes, which activates the UPR and decreases normal function or kills these cells [5,10,11].

At least two UPR signaling cascades [inositol-requiring 1 protein (IRE1) and PERK] are activated by missense PLP1 mutations, with induction of molecular chaperones, ATF4, CHOP, ATF3, GADD34 and caspase 12 in vitro, in mice and in PMD autopsy samples [5,12–15]. Curtailing PERK pathway signaling by deleting the *Chop* gene in *Plp1*-mutant mice reduces lifespan and increases cell death indicating that CHOP, or its targets, are adaptive and act as pro-survival factors [5]. This observation is most easily reconciled if the PERK pathway is viewed as a negative feedback loop to reduce cell metabolism and maintain homeostasis, such that disruption of the negative feedback leads to runaway metabolic stress and apoptosis. However, these data are at odds with studies in other cell types, which suggest that PERK signaling and induction of CHOP expression is a maladaptive pathway that promotes pathology and/or cell death [1,2].

The mechanism underlying the adaptive function of CHOP in oligodendrocytes is unknown, but may involve cell type-dependent specification of target genes. Indeed, differences in expression of CHOP targets in other cell types have been noted for oligodendrocytes [5], and identification of additional targets will provide a clearer picture of CHOP function in all cell types.

Multiple sclerosis

Although commonly considered a disease of myelin or oligodendrocytes with autoimmune etiology, recent debate has cast doubt on the immune system as the primary cause of multiple sclerosis (MS) [16]. In this light, recent studies by Popko and colleagues [4,17,18] suggest a provocative mechanism by which metabolic stress caused by interferon γ (IFN γ) release may mediate degenerative pathology in oligodendrocytes and engage the immune response.

In their initial report, Lin et al [4] demonstrated that ectopic secretion of IFN γ by astrocytes confers mild diffuse CNS hypomyelination in mice, which induces *Chop* gene expression in oligodendrocytes to suggest that the UPR is activated. Furthermore, they showed that curtailing PERK pathway activity in these mice (by deleting one copy of the *Perk* gene), does not alter *Chop* gene expression in oligodendrocytes, induces their apoptosis by several-fold, exacerbates CNS pathology and kills the mice by four weeks of age. In contrast, PERK deficiency in more mature mice did not alter sensitivity of oligodendrocytes to IFN γ . These results accord with earlier experiments showing *Chop* gene deletion exacerbates pathology in stressed oligodendrocytes [5], and emphasize the context-specific role of PERK in oligodendrocytes.

Subsequently, Lin and colleagues [18] deleted the *Gadd34* gene to curtail the PERK pathway, which marginally improved the IFN γ -mediated hypomyelinating phenotype even though “rescued” mice often died indeterminately by four weeks of age. Oligodendrocyte apoptosis was not analyzed and it is unclear if the lack of GADD34 increases cell survival. The absence of such data notwithstanding, these studies suggest that upstream components of the PERK pathway normally mediate adaptive responses to metabolic stress while downstream events, which are more focused on reversing the effects of PERK pathway signaling, are maladaptive. If so, then GADD34-mediated reactivation of global translation can be viewed as: a process that sensitizes cells to metabolic stress at the risk of losing homeostasis, but confers the evolutionary advantage of maximizing cell growth.

Vanishing white matter disease

Homozygous or compound heterozygous mutations in at least five genes cause the highly variable clinical phenotype of VWM [19]. Those genes that are best characterized include the five subunits of the eukaryotic initiation factor 2B (eIF2B) complex [reviewed by 3]. Because a number of mutations have been shown to reduce GTP exchange on eIF2 [19], the likely consequence for most patients is reduced global translation and constitutive PERK pathway activation [20]. This may render cells hypersensitive to metabolic stress and exacerbate normally sub-clinical pathophysiology to supra-threshold levels, as has been suggested for oligodendrocytes in vitro [21].

Superficially, constitutive PERK pathway signaling in VWM oligodendrocytes would not be expected to phenocopy the maladaptive effects associated with reducing PERK or CHOP expression. However, the mixed cell autonomy in the CNS (the UPR is activated in both oligodendrocytes and astrocytes) as well as the likely systemic effects of the disease with multiple tissues affected may obscure a detailed understanding of the pathophysiology [22, 19].

PNS myelin and Schwann cell pathology: Charcot-Marie-Tooth (CMT) disease

Similar to oligodendrocytes, Schwann cells synthesize myelin and face similar trafficking and quality control challenges; however, abundant myelin proteins such as protein zero (P₀) are unique to the PNS [23]. Nevertheless, mutations in these proteins induce ER stress and cause several CMT neuropathies [24]. P₀ mutations provide an excellent example of how UPR induction, and CHOP expression in particular, exhibits context- and cell-specific effects.

P₀ comprises approximately 50% of myelin proteins and is critical for membrane compaction during development and for long term myelin maintenance. Genetic evidence from patients and animal models suggests that a toxic gain-of-function mechanism accounts for the spectrum of P₀-related neuropathies [25,26]. For example, mice expressing endogenous P₀ in addition to a transgene-derived mutant P₀ lacking serine 63 (P₀S63del) manifest a demyelinating neuropathy that phenocopies the corresponding CMT1B human neuropathy.

The P₀S63del protein is not incorporated into myelin, but is retained in the ER and induces a UPR and CHOP [6,25]. In contrast to other UPR diseases with primary cell death [2], Schwann cell apoptosis is not induced, and P₀S63del nerves show neither an obvious reduction in Schwann cell number nor a phenotype typical of extensive Schwann cell death. Rather, apoptosis in P₀S63del mice rises weeks later and more closely parallels the appearance of demyelinated axons [6]. Consistent with these data, CHOP is usually detected in non-pyknotic Schwann cells with intact myelin sheaths (Figure 2), suggesting it may induce demyelination leading to secondary Schwann cell death. Nevertheless, ablation of the *Chop* gene in P₀S63del mice ameliorates demyelination and rescues the motor deficit, which indicates that the UPR is pathogenic and CHOP is maladaptive. Together, these data indicate that CHOP activity in Schwann cells is distinct from other cell types and that UPR activation does not imply cell death [2,27], as demonstrated for oligodendrocytes [5].

In the absence of a clear link between CHOP and apoptosis in Schwann cells, how does CHOP interfere with myelin in P₀S63del nerves? An attractive notion is that CHOP target genes disrupt important aspects of myelinogenesis in Schwann cells. Thus, by promoting eIF2 α dephosphorylation, GADD34 may reverse stress-induced changes in the translation of specific mRNAs, causing toxicity [28].

Conclusions and future directions

An intriguing aspect of the pathophysiology of UPR-mediated disease in myelinating cells is the resistance of stressed Schwann cells, and the sensitivity of stressed oligodendrocytes, to apoptosis [4–6]. Although these studies include only qualitative assessments to suggest that the extent of UPR induction is similar in each cell type, it is tempting to speculate that the likelihood of an apoptotic response may reflect the range of homeostatic mechanisms available to individual cells. Thus, most studies acknowledge the importance of the IRE1, PERK and ATF6 pathways, but few consider other adaptive responses such as dedifferentiation (Figure 3).

In this regard, Tsang and colleagues [29] show that a nonsense mutation in the collagen 10 (*Col10a1*) gene induces the UPR in chondrocytes leading to dedifferentiation, which reduces mutant gene expression and maintains cell viability. Interestingly, Schwann cells readily dedifferentiate after nerve injury [30], and the hypomyelinating phenotype of P₀S63del mice in the absence of significant apoptosis suggests that these cells too may ameliorate metabolic stress through dedifferentiation [24]. Perturbed differentiation of oligodendrocytes also has been suggested as a cause of the hypomyelinating phenotype in *Plp1* mutants [31]; however, these cells rarely dedifferentiate [32], and subsequent studies show they undergo robust apoptosis upon expressing mutant PLP1 [10] and are likely replaced by differentiating progenitors.

To resolve an apparent contradiction that the UPR is an adaptive response that nonetheless executes maladaptive programs, several ideas have emerged in recent years. Walter and colleagues [27] suggest from in vitro data that dual activation of IRE1 and PERK pathways promotes an adaptive response, whereas unilateral activation of PERK is maladaptive. Whether this notion applies to myelinating glia in vivo is unclear. Although both pathways operate concurrently in nervous tissue [4–6,12], it is not known if they act simultaneously in single cells.

Somewhat similarly, Rutkowski and Kaufman [2] postulate that temporal shifts in the response modulate which of the negative feedback loops are active, and their extent of activation, which yields adaptive or maladaptive UPR outputs. Alternatively, data from oligodendrocytes suggests that activating the UPR is an adaptive response, whereas inactivating the UPR may be maladaptive (Figure 1). Of course, a simpler concept may be that adaptive UPR pathways are independent of maladaptive pathways that may supercede the UPR. Whichever is the case, these ideas provoke a plethora of testable hypotheses for the elucidation of UPR function and, particularly, for the development of in vivo paradigms with which to undertake quantitative and mechanistic analyses.

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Glossary

ATF4	constitutively expressed mRNA. An open reading frame upstream of ATF4 is translated under non-stress conditions. During stress, ATF4 is translated
ATF6	is constitutively expressed and localized to the ER membrane. During stress, ATF6 reaches the Golgi where proteolytic cleavage releases the active cytosolic transcription factor
CMT	a spectrum of hereditary motor and sensory peripheral neuropathies caused by mutations in a number of genes. CMT1B is associated with mutations in the <i>Myelin Protein Zero (MPZ)</i> gene
eIF2	a GTP binding protein and regulatory component of ribosome assembly. Forms a trimolecular complex with GTP and the initiator methionine tRNA to generate the pre-initiation complex
eIF2B	the GTP exchange factor (GEF) for eIF2 with five subunits: eIF2B1,2,4 regulate the GEF and bind eIF2 α or eIF2 α P to activate or suppress GTP exchange. The eIF2B3 and eIF2B5 subunits form the catalytic domain
eIF2α	regulatory subunit for GTP exchange with eIF2B. Phosphorylation (eIF2 α P) by PERK inhibits the GEF activity of eIF2B
ERAD	Unfolded protein intermediates are dislocated from the ER, polyubiquitinated and hydrolyzed by the proteasome
GADD34	the regulatory subunit for protein phosphatase 1 (PP1). De-phosphorylates eIF2 α P to reverse attenuation of global translation
IFNγ	a cytokine that stimulates innate and acquired immune responses. Ectopic expression exacerbates inflammatory and autoimmune responses
MS	a progressive neurodegenerative CNS disease characterized by demyelinating foci in white and gray matter regions. Oligodendrocyte and axon loss within the lesions. Immune system involvement in myelinated tracts. IFN γ activates the ER stress in oligodendrocytes and may kill these cells. Neuron death caused by transection of demyelinated axons

PERK	an ER-resident membrane protein that monitors protein flux. Is normally monomeric, but homodimerizes during stress and phosphorylates eIF2 α
PMD	this disease is principally caused by deletions, duplications and coding region mutations in the <i>PLP1</i> gene. Clinical phenotype is broad, from mild SPG2-like symptoms to severe immobility and shortened lifespan. Coding region mutations activate the UPR in oligodendrocytes. The PNS is spared
SPG2	is caused by <i>PLP1</i> gene mutations conferring mild progressive disease characterized by lower limb spasticity. The PNS is spared
UPR	a series of signaling pathways triggered by endoplasmic reticulum-resident receptors :PERK, IRE1 and ATF6
VWM	a disease caused by mutations in eIF2B subunits. Clinical symptoms typically manifest following mild infections, fever or injury

References

1. Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol* 2007;8:519–529. [PubMed: 17565364]
2. Rutkowski DT, Kaufman RJ. That which does not kill me makes me stronger: adapting to chronic ER stress. *Trends Biochem Sci* 2007;32:469–476. [PubMed: 17920280]
3. Pavitt GD. eIF2B, a mediator of general and gene-specific translational control. *Biochem Soc Trans* 2005;33:1487–1492. [PubMed: 16246152]
4. Lin W, Harding HP, Ron D, Popko B. Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferon-gamma. *J Cell Biol* 2005;169:603–612. [PubMed: 15911877]
5. Southwood CM, Garbern J, Jiang W, Gow A. The unfolded protein response modulates disease severity in Pelizaeus-Merzbacher disease. *Neuron* 2002;36:585–596. [PubMed: 12441049]
- 6•. Pennuto M, Tinelli E, Malaguti M, Del Carro U, D'Antonio M, Ron D, Quattrini A, Feltri ML, Wrabetz L. Ablation of the UPR-mediator CHOP restores motor function and reduces demyelination in Charcot-Marie-Tooth 1B mice. *Neuron* 2008;57:393–405. [PubMed: 18255032]
This paper reports induction of the UPR in CMT1B neuropathy for the first time and demonstrates genetically that CHOP expression is maladaptive, but causes Schwann cell dysfunction (demyelination) not cell death
7. Lin W, Popko B. Endoplasmic reticulum stress in disorders of myelinating cells. *Nat Neurosci* 2009;12:379–385. [PubMed: 19287390]
8. Duncan, ID. Dissection of the phenotype and genotype of the X-linked myelin mutants. In: Duncan, ID.; Skoff, RP.; Colman, DR., editors. *Myelination and Dysmyelination*. New York: Academy of Sciences; 1990. p. 110-121. *Ann N Y Acad Sci* 605
9. Gow, A. Protein misfolding as a disease determinant. In: Lazzarini, RA., editor. *Myelin Biology and Disorders*. Elsevier; 2004. p. 877-885. p. 1
10. Gow A, Southwood CM, Lazzarini RA. Disrupted proteolipid protein trafficking results in oligodendrocyte apoptosis in an animal model of Pelizaeus-Merzbacher disease. *J Cell Biol* 1998;140:925–934. [PubMed: 9472043]
11. Gow A, Friedrich VL, Lazzarini RA. Many naturally occurring mutations of myelin proteolipid protein impair its intracellular transport. *J Neurosci Res* 1994;37:574–583. [PubMed: 7518006]
12. Southwood CM, Gow A. Molecular mechanisms of disease stemming from mutations in the proteolipid protein gene. *Micros Res Tech* 2001;52:700–708.
- 13•. Sharma R, Gow A. Minimal role for caspase 12 in the unfolded protein response in oligodendrocytes in vivo. *J Neurochem* 2007;101:889–897. [PubMed: 17394578] Although caspase 12 expression is induced at the levels of mRNA and protein in *Plp1* mutant mice, its absence does not alter the levels

of apoptosis occurring in response to metabolic stress. Thus, caspase 12 is not an obligatory UPR caspase in vivo

14. Swanton E, High S, Woodman P. Role of calnexin in the glycan-independent quality control of proteolipid protein. *Embo J* 2003;22:2948–2958. [PubMed: 12805210]
15. Sharma R, Jiang H, Zhong L, Tseng J, Gow A. Minimal role for activating transcription factor 3 in the oligodendrocyte unfolded protein response in vivo. *Journal of Neurochemistry* 2007;102:1702–1713.
16. Trapp BD, Nave KA. Multiple sclerosis: an immune or neurodegenerative disorder? *Annu Rev Neurosci* 2008;31:247–269. [PubMed: 18558855]
- 17•. Lin W, Bailey SL, Ho H, Harding HP, Ron D, Miller SD, Popko B. The integrated stress response prevents demyelination by protecting oligodendrocytes against immune-mediated damage. *J Clin Invest* 2007;117:448–456. [PubMed: 17273557] This paper provides further evidence that the PERK pathway is adaptive in oligodendrocytes in a variety of normal and pathological contexts. In this case, cytokine activation of PERK prior to onset of experimental allergic encephalitis in mice, a model of MS, was protective which has therapeutic implications
- 18••. Lin W, Kunkler PE, Harding HP, Ron D, Kraig RP, Popko B. Enhanced integrated stress response promotes myelinating oligodendrocyte survival in response to interferon-gamma. *Am J Pathol* 2008;173:1508–1517. [PubMed: 18818381] Popko and colleagues provide evidence that genetic or pharmacological inhibition of GADD34 and its reversal of eIF2alpha phosphorylation is adaptive in myelinating oligodendrocytes challenged by IFN γ , consistent with the idea that PERK activation is adaptive, and GADD34 activation maladaptive in oligodendrocytes
19. Fogli A, Boespflug-Tanguy O. The large spectrum of eIF2B-related diseases. *Biochem Soc Trans* 2006;34:22–29. [PubMed: 16246171]
20. van Kollenburg B, van Dijk J, Garbern J, Thomas AA, Scheper GC, Powers JM, van der Knaap MS. Glia-specific activation of all pathways of the unfolded protein response in vanishing white matter disease. *J Neuropathol Exp Neurol* 2006;65:707–715. [PubMed: 16825957]
21. Kantor L, Pinchasi D, Mintz M, Hathout Y, Vanderver A, Elroy-Stein O. A point mutation in translation initiation factor 2B leads to a continuous hyper stress state in oligodendroglial-derived cells. *PLoS One* 2008;3:e3783. [PubMed: 19023445]
22. Dietrich J, Lacagnina M, Gass D, Richfield E, Mayer-Proschel M, Noble M, Torres C, Proschel C. EIF2B5 mutations compromise GFAP+ astrocyte generation in vanishing white matter leukodystrophy. *Nat Med* 2005;11:277–283. [PubMed: 15723074]
23. Scherer SS, Wrabetz L. Molecular mechanisms of inherited demyelinating neuropathies. *Glia* 2008;56:1578–1589. [PubMed: 18803325]
24. D'Antonio M, Feltri ML, Wrabetz L. Myelin under stress. *J Neurosci Res.* 2009;100:1002/jnr.22066
25. Wrabetz L, D'Antonio M, Pennuto M, Dati G, Tinelli E, Fratta P, Previtali S, Imperiale D, Zielasek J, Toyka K, et al. Different intracellular pathomechanisms produce diverse Myelin Protein Zero neuropathies in transgenic mice. *J Neurosci* 2006;26:2358–2368. [PubMed: 16495463]
26. Martini R, Zielasek J, Toyka K, Giese K, Schachner M. Protein zero (P0)-deficient mice show myelin degeneration in peripheral nerves characteristic of inherited human neuropathies. *Nature Genet* 1995;11:281–286. [PubMed: 7581451]
- 27•. Lin JH, Li H, Zhang Y, Ron D, Walter P. Divergent effects of PERK and IRE1 signaling on cell viability. *PLoS One* 2009;4:e4170. [PubMed: 19137072] This study employs ingenious extended, single activation of PERK or IRE1 (uncoupled from protein misfolding) in cultured cells to demonstrate that the quantitative balance between PERK and IRE1 signals may determine death versus survival fates, respectively
28. Marciniak SJ, Yun CY, Oyadomari S, Novoa I, Zhang Y, Jungreis R, Nagata K, Harding HP, Ron D. CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. *Genes Dev* 2004;18:3066–3077. [PubMed: 15601821]
- 29••. Tsang KY, Chan D, Cheslett D, Chan WC, So CL, Melhado IG, Chan TW, Kwan KM, Hunziker EB, Yamada Y, et al. Surviving endoplasmic reticulum stress is coupled to altered chondrocyte differentiation and function. *PLoS Biol* 2007;5:e44. [PubMed: 17298185] One of the first examples of incomplete differentiation/dedifferentiation occurring in response to a UPR in the absence of

apoptosis. This study raises the possibility that some cell types can ameliorate maladaptive effects of UPR signaling by dedifferentiating.

30. Parkinson DB, Bhaskaran A, Arthur-Farraj P, Noon LA, Woodhoo A, Lloyd AC, Feltri ML, Wrabetz L, Behrens A, Mirsky R, et al. c-Jun is a negative regulator of myelination. *J Cell Biol* 2008;181:625–637. [PubMed: 18490512] This paper shows that Krox 20 and c-Jun have a reciprocally antagonistic function and regulation during development; c-Jun is predominant as part of an active program of dedifferentiation of Schwann cells
31. Gardinier MV, Macklin WB. Myelin proteolipid protein gene expression in jimpy and jimpy(msd) mice. *J Neurochem* 1988;51:360–369. [PubMed: 2455772]
32. Franklin, RJ.; Goldman, JE. Remyelination by endogenous glia. In: Lazzarini, RA., editor. *Myelin Biology and Disorders*. Vol. 1. Elsevier Academic Press; 2004. p. 173-196.

Figure 1. Major components of the PERK pathway in myelinating glia

Changes in protein flux through the secretory pathway trigger signaling from ER-resident receptors including IRE1, ATF6 and PERK. The major components detailed in the text are shown for the PERK pathway, and the schematic summarizes the results of several *in vivo* studies in oligodendrocytes. Thus, perturbing the functions of PERK, eIF2 or CHOP exacerbates disease symptoms. These components normally fulfill adaptive functions to enable cells to re-establish homeostasis (green). In contrast, perturbing the function of GADD34 reduces disease symptoms, indicating that this protein normally serves to increase cell sensitivity to the effects of protein misfolding. As such, this activity can be, perhaps paradoxically, interpreted as maladaptive; however, the greater risk of apoptosis is offset because the cell is able to grow and function effectively.

Figure 2. Persistent CHOP expression promotes demyelination, but does not directly kill Schwann cells

Immunostaining reveals CHOP (red) in DAPI-positive Schwann cell nuclei (blue) in cross sections of P₀S63del (B), but not wild type (A) sciatic nerves [6]. CHOP-positive Schwann cell nuclei are not pyknotic and are associated with myelin sheaths (green).

Figure 3. a potential role for dedifferentiation to ameliorate metabolic stress in the absence of apoptosis

A. Developmental studies suggest that upon differentiation from progenitor cells, oligodendrocytes rarely dedifferentiate into a non-myelinating proliferative precursor [32]. In PMD/SPG2, oligodendrocytes may only be able to alleviate metabolic stress by signaling through the UPR. This unidirectional approach to maintaining homeostasis may increase the risk of apoptosis through various maladaptive pathways. B. Unlike oligodendrocytes, Schwann cells readily switch between a differentiated, myelinating phenotype and a dedifferentiated, non-myelinating phenotype [30]. Thus if the UPR is activated, these cells could utilize UPR signaling and dedifferentiation to alleviate stress.