



ER Dynamics and Derangement in Neurological Diseases

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The endoplasmic reticulum (ER) is a morphologically dynamic organelle containing different membrane subdomains with distinct cellular functions. Numerous observations have revealed that ER stress response induced by disturbed ER homeostasis is linked to various neurological/neurodegenerative disorders. In contrast, recent findings unveil that ER structural derangements are linked to the progression of several neurological diseases. The derangements involve two distinct, and likely opposing pathways. One is dysfunction of ER dynamics machinery, leading to disruption of ER network organization. Another one is facilitation of pre-existing machinery, leading to generation of markedly-ordered *de novo* membranous structure. Restoring the ER network can be the effective way toward the cure of ER-deranged neurological disorders.

Keywords: endoplasmic reticulum, ER architecture, ER dynamics, neurological disease, neurodegeneration, NF-Y

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INTRODUCTION

Endoplasmic reticulum (ER) is a continuous membrane organelle dispersing throughout the cells. It consists of two differentially shaped membranous domains; the nuclear envelope, a highly regulated membrane barrier that separates the nucleus from the cytoplasm, and the peripheral ERs including ribosome-studded rough ER (RER) and ribosome-free smooth ER (SER) (**Figure 1**). The RER plays a key role in synthesis and transport of secretory/membrane proteins. The SER is critical for synthesis of lipids / sterols, storage and regulated release of calcium, and metabolism and detoxification. These peripheral ERs are highly dynamic and change their shapes and volumes on the demand of cellular needs (Federovitch et al., 2005; Park and Blackstone, 2010; Westrate et al., 2015).

ER dysfunction causes deleterious effects on the cells and is associated with many diseases including various neurological/neurodegenerative disorders. The major pathway involved in this is ER stress responses induced by disturbance of ER homeostasis due to protein misfolding and aggregation (Matus et al., 2011; Remondelli and Renna, 2017). In contrast, recent findings highlight another ER abnormalities associated with ER morphological alteration in neurological diseases. These are mainly caused by dysregulations of ER-resident membrane proteins. In this review, we discussed the ER dynamics and its derangement in neuropathogenesis.

Peripheral ER Organization and Dynamics

The peripheral ERs are morphologically subdivided into two domains, ER sheets and tubules (**Figure 1**). The sheets mainly located in perinuclear region and tend to be studded with ribosomes (RER), whereas tubules form cytoplasmic network and are largely devoid of ribosomes (SER). Different sets of proteins are involved in the organization of these distinct ER membrane domains (**Figure 2**; Park and Blackstone, 2010; Chen et al., 2013; Westrate et al., 2015). In the sheets, one of the key regulators is stubbed ribosome, which is elegantly shown by the experiment using two

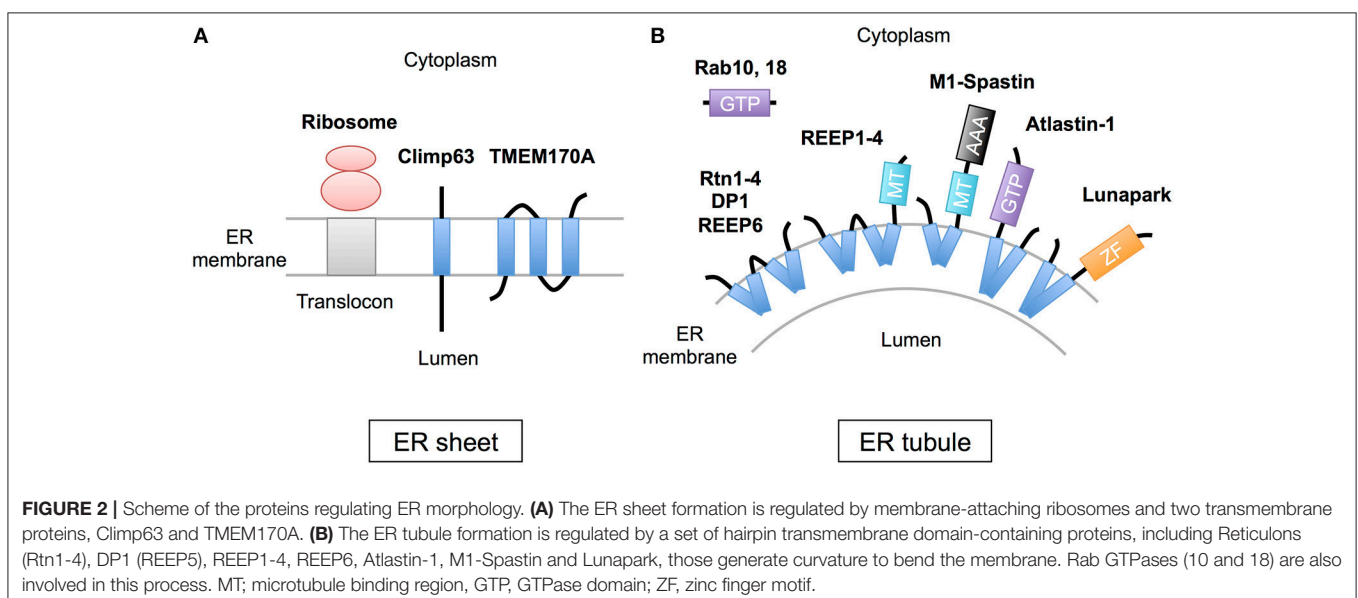
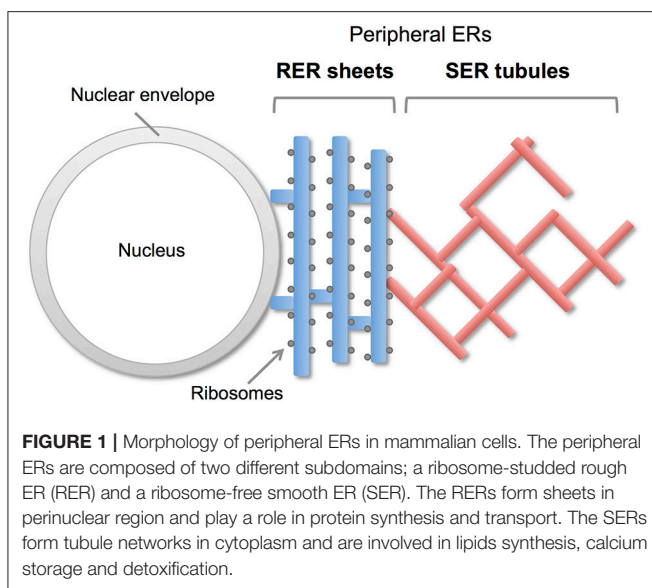
translation inhibitors, puromycin or cycloheximide; the ER sheets are disrupted by puromycin that quickly dissociates polysomes from ER membranes, but not by cycloheximide that stabilizes ribosomal association with translocons, in cultured cells (Puhka et al., 2007). Two transmembrane protein Climp63 and TMEM170A are also shown to be important regulators for RER sheet formation; knockdown of each one decreased ER sheets whereas its overexpression increased them (Shibata et al., 2010; Christodoulou et al., 2016). As for TMEM170A, its localization to nuclear envelopes and regulation of nuclear morphology are also reported (Christodoulou et al., 2016). Thus, the ER sheets are organized by different types of proteins (**Figure 2**).

On the contrary, the ER tubules are generated by a set of specific membrane proteins that contain one or two “hairpin” transmembrane domains. This domain is inserted

into outer leaflet of the membrane bilayer and suggested to generate curvature to bend the membrane (**Figure 2**; Park and Blackstone, 2010; Chen et al., 2013; Westrate et al., 2015). The membrane proteins include Reticulons (Rtn1-4), DP1 (deleted in polyposis locus 1; also known as REEP5), other REEPs (receptor expression-enhancing proteins; REEP1-4 and 6), Atlastin-1, M1-Spastin and Lunapark. Among them, Reticulons, DP1 and Atlastin-1 are extensively analyzed and shown to be required for formation of ER tubular network *in vitro* (Hu et al., 2008; Wang et al., 2016; Powers et al., 2017) and in cultured cells (Voeltz et al., 2006; Hu et al., 2009). These three proteins interact with each other (Hu et al., 2009), and form immobile oligomer complex in the tubules (Shibata et al., 2008; Orso et al., 2009). Complex formation of REEP1 with Atlastin-1 and M1-Spastin and its contribution of ER tubule formation are also reported (Evans et al., 2006; Park et al., 2010). Thus, interconnected interactions of these membrane-inserting proteins mediate the ER tubule formation. Atlastin-1 and Lunapark also induce homotypic ER fusion to generate branched tubules (Orso et al., 2009; Chen et al., 2012, 2015). Binding to microtubule cytoskeleton through REEP1-4 and M1-spastin is further involved in establishment and maintenance of complicated tubular network (Park and Blackstone, 2010; Westrate et al., 2015).

Disruption of ER Dynamics in Neurological Diseases

Notably, some of the ER tubule proteins have been shown to be mutated in hereditary spastic paraplegia (HSP), a group of genetic disorders caused by a length-dependent, distal axonopathy of corticospinal motor neurons, leading to lower limb spasticity and weakness. Currently, over 40 different genetic loci (SPG1–45) are reported (Blackstone et al., 2011; Lo Giudice et al., 2014). Despite the large number of loci, about 60% of HSP patients harbor pathogenic mutations in one of three proteins: Spastin (SPG4), Atlastin-1 (SPG3A), or REEP1 (SPG31), all of which are the regulators of ER tubule formation as described



above. In addition, another ER tubule protein Rtn2 is also mutated in SPG12 patients. Thus, these SPG proteins are critical for motor neuron integrity *in vivo*. Indeed, knockdown of Spastin or Atlastin-1 in zebrafish induces axonal degeneration in motor neurons and locomotion defects (Butler et al., 2010; Fassier et al., 2010; Patten et al., 2014). In mice, mutation in Spastin or REEP1 causes progressive axonal degeneration of corticospinal motor neurons and motor defects (Tarrade et al., 2006; Beetz et al., 2013; Renvoise et al., 2016). Furthermore, peripheral ER complexity decreases in primary motor neurons of REEP1 mutant mice (Beetz et al., 2013). These observations suggest that these SPG proteins are necessary for axonal development and/or maintenance probably by modulating ER architecture in motor neurons. Because Spastin, Atlastin-1, and REEP1 are co-enriched in axonal growth cones in cultured neurons (Park et al., 2010), they may regulate axonal growth by modulating ER tubule network dynamics.

The other factors involved in the ER tubule formation are Rab GTPases, central regulators of vesicle budding, motility, and fusion (Figure 2). Two Rab GTPases, Rab10, and Rab18, are shown to localize to ER tubules and its dysfunction results in ER tubule disorganization in cultured cells (English and Voeltz, 2013; Gerondopoulos et al., 2014). Notably, loss-of-function mutations of Rab18 or its regulator RabGAP cause Warburg Micro Syndrome, a rare autosomal recessive genetic disorder characterized by severe eye and brain abnormalities (Bem et al., 2011). Knockdown of Rab18 in zebrafish causes developmental abnormalities including microphthalmia and microcephaly (Bem et al., 2011). In addition, knockdown of Rab10 or Rab18 induces defects in neuronal differentiation in mouse brain cortex (Wang et al., 2011; Wu et al., 2016). These observations reveal critical roles of these Rab GTPases in neuronal development *in vivo*.

An ER membrane protein FAM134B is also linked to a neurological disease named hereditary sensory and autonomic neuropathy (HSAN) (Kurth et al., 2009). Interestingly, this protein is shown to be an autophagy receptor to mediate degradation of ER through autophagic system. This phenomenon is called ER-phagy, which is considered to be involved in ER homeostasis (Khaminets et al., 2015). Being its localization mainly to ER sheets, FAM134B is thought to be an ER sheet-specific autophagy receptor. Recently, an ER tubule protein Rtn3 is identified as another ER-phagy receptor, which induce fragmentation and autophagic degradation of ER tubules independently of FAM134B (Grumati et al., 2017). Thus, FAM134B and Rtn3 may regulate different ER membranes to regulate overall ER homeostasis.

The ER Tubule Network and Neurodegenerative Diseases

The ER tubules are interacting with other membranous organelles such as mitochondria, plasma membrane, peroxisomes and lysosomes. The mitochondria-associated ER membrane (MAM) mediates several fundamental cellular processes including calcium exchange, phospholipid exchange, intracellular trafficking and autophagy. The ER-mitochondria associations through MAM are shown to be disrupted in several

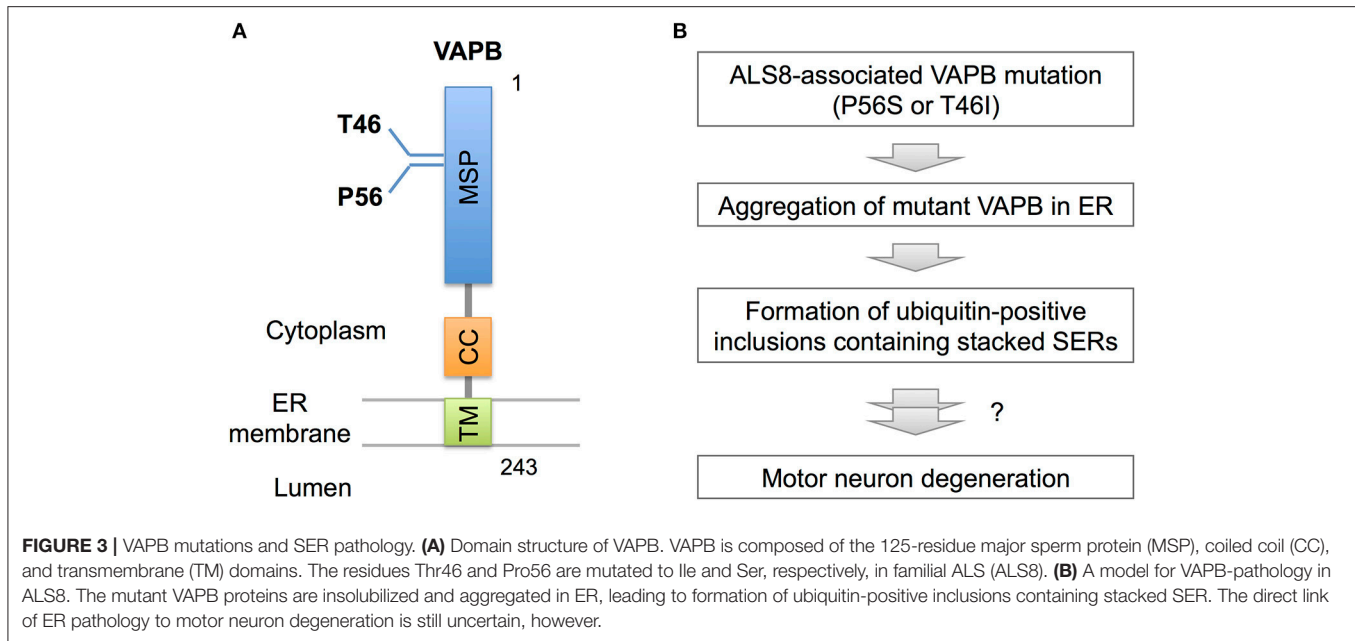
neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease and amyotrophic lateral sclerosis with associated frontotemporal dementia (ALS/FTD), resulting in alteration in cellular functions regulated by MAM (Paillusson et al., 2016).

Direct implications of ER tubule proteins in disease pathogenesis have been reported. In superoxide dismutase 1 (SOD1) G93A transgenic mouse, a model for ALS, depletion of Rtn4 accelerates disease onset and progression possibly by disrupting normal distribution of protein disulfide isomerase (PDI), suggesting protective role of Reticulon in motor neuron degeneration (Yang et al., 2009). As for AD, Rtn3 binds to and colocalizes with BACE1, a beta-secretase involved in amyloid precursor protein (APP) cleavage and amyloid beta production. Interestingly, overexpression of Rtn3 reduces the production of amyloid beta while its knockdown enhances it in cultured cells. Furthermore, Rtn3 blocks BACE1 interactions with APP, suggesting that the Reticulon negatively modulates BACE1 activity and amyloid beta production (He et al., 2004). In addition, enhanced expression of Rtn3 suppresses amyloid plaque formation in transgenic mice expressing mutants for APP and presenilin-1 (Shi et al., 2009). In contrast to these beneficial effects, Rtn3 is found to be aggregated and accumulated in dystrophic neurites, named as Rtn3 immunoreactive dystrophic neurites (RIDNs) in brains of AD cases and mice brains expressing mutant APP. Furthermore, Rtn3 transgenic expression impairs spatial learning and memory as well as synaptic plasticity in mice, implying that RIDNs potentially contribute to AD cognitive dysfunction (Hu et al., 2007). Thus, Rtn3 may bidirectionally regulate AD pathogenesis *in vivo*.

Biogenesis of Highly-Ordered ERs, the Stacked SERs

In addition to the tubular architecture as described above, the SER is known to form highly-organized membranous structures where cisternae are stacked with ordered arrays (Federovitch et al., 2005; Borgese et al., 2006). This "stacked SER" is observed in the cells highly demanding SER-related functions such as lipid biosynthesis and drug metabolism. These include adrenal cells that produce large amount of sterol lipids, and liver cells of animal treated with phenobarbital (Feldman et al., 1981; Federovitch et al., 2005). Treatment of statins (cholesterol synthesis inhibitors) also leads to stacked SER formation by induced expression of an ER-resident enzyme, hydroxy-methylglutaryl (HMG)-CoA reductase (Singer et al., 1988; Borgese et al., 2006). Interestingly, overexpression of ER resident membrane proteins such as cytochrome b(5), P450, aldehyde dehydrogenase, Sec61 and Calnexin in cultured cells is shown to be sufficient for stacked SER formation (Yamamoto et al., 1996; Snapp et al., 2003; Korkhov and Zuber, 2009). Thus, load of ER-resident membrane proteins is one of the factors for stacked SER biogenesis.

As for the molecular mechanism, selective activation of ATF6 and following lipid synthesis are suggested to be involved in stacked SER generation upon cytochrome b(5)



expression (Maiuolo et al., 2011). Because of no inductions of ER chaperone expression, XBP1 splicing or eIF2-alpha phosphorylation, the usual unfolded protein response (UPR) pathway may not be involved in ATF6-dependent pathway. Knockdown of Syntaxin 18, a SNARE component involved in ER-Golgi transport and ER-network organization, also induces stacked SER formation (Iinuma et al., 2009). Furthermore, knockdown of a membrane protein Yip1A, which cycles between ER and early Golgi, induces formation of stacked SER (Dykstra et al., 2010). A compound phenyl-2-decanoyl-amino-3-morpholino-1-propanol-hydrochloride (PDMP) that blocks membrane transport from ER to Golgi also induces generation of this type of ER (Sprocati et al., 2006). Experiments using several compounds further suggested that altering ionic homeostasis in ER is also an inducer of stacked SER formation independently of known UPR pathways (Varadarajan et al., 2012, 2013). Notably, the stacked SER formation often accompanies Golgi fragmentation and delay of ER export (Iinuma et al., 2009; Dykstra et al., 2010; Varadarajan et al., 2012). These observations suggest close relationship of ER-Golgi transport machineries, rather than canonical UPR pathways, to stacked SER biogenesis.

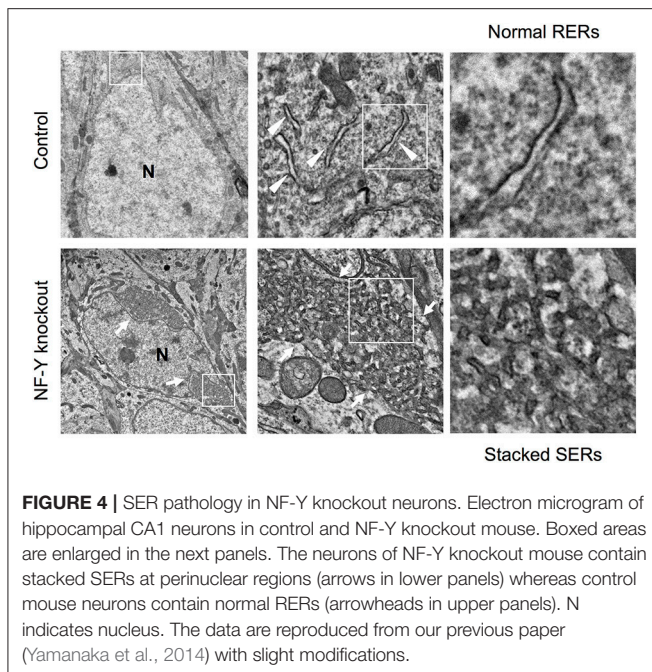
Despite the drastic alterations of ER and Golgi architectures, there is no report describing distinct reduction of cell viability. Importantly, the ER structure is reversible because depletion of the compounds such as PDMP leads to disappearance of stacked SER (Sprocati et al., 2006; Varadarajan et al., 2012). Thus, the stacked SER formation may not be the toxic inducer for cells but is suggested to be a novel stress response to cope with overload of ER membrane proteins independently of usual UPR pathways.

Stacked SER Pathologies in Neurological Diseases

Recent observations, however, indicate pathogenic significance of stacked SER in neurological diseases. In familial ALS

(ALS8), an ER-resident membrane protein, vesicle-associated membrane protein-associated protein B (VAPB) is mutated (Figure 3; Nishimura et al., 2004). Overexpressed mutant VAPB protein in cultured cells is insolubilized and aggregated in ER, leading to formation of ubiquitin-positive inclusions containing stacked SERs (Figure 3; Teuling et al., 2007; Fasana et al., 2010). In cultured neurons, the mutant VAPB overexpression induces Golgi fragmentation and cell death (Teuling et al., 2007). Furthermore, in VAPB mutant-transgenic mice ubiquitin-positive inclusions associated with stacked SER are developed in motor neurons (Tudor et al., 2010; Aliaga et al., 2013; Kuijpers et al., 2013; Qiu et al., 2013), and furthermore progressive loss of corticospinal motor neurons is observed in some of mice lines (Aliaga et al., 2013). Although the neurotoxic effect of mutant VAPB is still controversial because other transgenic mice lines do not show neuronal loss or motor phenotypes (Tudor et al., 2010; Kuijpers et al., 2013; Qiu et al., 2013), VAPB mutant knock-in mice are shown to display slow progression of motor behavior defects (Larroquette et al., 2015), suggesting a certain involvement of VAPB mutation on motor neuron dysfunction.

Torsion dystonia-1 (DYT1) is the most common inherited dystonia characterized by involuntary muscle contractions and abnormal postures, which is caused by mutation in TorsinA, an ER glycoprotein belonging to AAA family of proteins (Ozelius et al., 1997). The mutant TorsinA forms cytoplasmic inclusions containing stacked SER in cultured neuronal cells (Hewett et al., 2000; Gonzalez-Alegre and Paulson, 2004). In peripheral nervous system, mutation in peripheral myelin protein 22 (PMP22) is linked to Charcot-Marie-Tooth disease, a sensorineural peripheral polyneuropathy. PMP22 is expressed in Schwann cells and its mutation induces formation of cytoplasmic inclusion containing mutant protein in association with stacked SER formation (Dickson et al., 2002). These observations further provide the pathological significance of cytoplasmic inclusions containing stacked SER in neurological diseases.



A novel mouse model for stacked SER pathology in brain neurons was recently established (Yamanaka et al., 2014, 2016). Importantly, it does not involve disease-associated gene mutation but just caused by inactivation of CCAAT-binding factor NF-Y, a ubiquitous transcription factor shown to be affected in polyglutamine diseases (Yamanaka et al., 2008; Katsuno et al., 2010; Huang et al., 2011). The neuron-specific knockdown of NF-Y induces insolubilization of various membrane proteins including Calnexin, Reticulon, Atlastin-1, APP and Carboxypeptidase E together with ubiquitin and p62/Sqstm1, all of which are accumulated on ER (Yamanaka et al., 2014, 2016). It also accompanies perinuclear accumulation of ribosome-free SERs and Golgi disassembly (Figure 4). Chromatin immunoprecipitation identifies several genes involved in protein folding in ER and ER-associated degradation

(ERAD) as targets of NF-Y, suggesting a critical role of NF-Y in ER protein homeostasis to maintain normal ER architecture in brain neurons.

CONCLUSIONS

Among the peripheral ERs, SERs appear to be deranged in several neurological diseases through at least two pathways. One is disturbance of peripheral ER network in the diseases such as HSPs, which is caused by mutations of genes required for SER tubule organization. The SER network disruption may also be involved in Alzheimer's disease and ALS pathogenesis. Another one is development of highly-ordered stacked SER in the diseases such as ALS8, which is caused by overload of misfolded and insolubilized proteins on ER membranes. NF-Y-mediated gene regulatory pathway can be involved in this atypical ER pathogenesis. Finding the way to restore SER networks is a future challenging issue toward the cure of these ER-related neurological disorders.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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