Brain Research 1648 (2016) 527–529

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres

Editorial

PREFACE: Divergent roles of ER stress in neurodegeneration and brain disorders

Neurodegenerative diseases represent a major increasing burden to our aging society. Inherited and sporadic forms of neurodegenerative disorders arise mid to late in life by selectively affecting specific neuronal populations within defined regions of the central nervous system (CNS). The large majority of neurodegenerative diseases occur sporadically and primarily affect cognition (Alzheimer's disease and frontotemporal lobar degeneration) or movement control (Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, motor neuron diseases) or both (dementia with Lewy bodies and corticobasal degeneration). A minor proportion of all NDs are inherited and occur in mid-life (Double et al., 2010).

The pathogenesis of neurodegenerative diseases primarily involves the abnormal accumulation and aggregation of specific misfolded proteins in distinct regions of the brain, and are classified as protein misfolding disorders (PMDs) (Davies et al., 1997; Martindale et al., 1998; Koo et al., 1999; Takalo et al., 2013). Furthermore, genetic mutations or environmental factors can also provoke or enhance protein misfolding and aggregation in PMDs (Takalo et al., 2013; Soto, 2003). Proteins that are known to aggregate and accumulate in PMDs such as amyloid β, Tau, α-synuclein, TDP-43, polyglutamine expanded proteins, among others, possess very unstable three-dimensional structures in physiological conditions and are prone to misfolding (Soto, 2012). The maintenance of the cellular proteome is a prerequisite for optimal cell functioning and cell survival, and the flux of unfolded polypeptide chains entering the endoplasmic reticulum (ER) to be folded by chaperones is varying. Therefore, cells constantly sense and adjust the ER folding capacity in a dynamic way through an integrated machinery known as the proteostasis network (Balch et al., 2008; Hetz et al., 2015). In scenarios where protein-folding demands are too high for the cell, then the accumulation of misfolded or aggregated proteins within ER lumen triggers a condition termed as ER stress (Rivas et al., 2015).

ER stress is a salient feature of specialized secretory cells and is observed in many human diseases including cancer, diabetes, obesity and neurodegeneration (Oakes and Papa, 2015; Ron and Walter, 2007). ER stress is initiated by the activation of the unfolded protein response (UPR), an integrated signal transduction pathway that transmits information about the protein folding status at the ER to the nucleus and cytosol to restore proteostasis. Conversely, cells undergo apoptosis if these mechanisms of adaptation and survival are insufficient to handle the unfolded protein load. Three major pathways mediate adaptation to ER stress, initiated by the sensors PERK, IRE1 and ATF6. These signal transduction pathways reset gene expression by controlling specialized downstream transcription factors that virtually modulate all aspects of the secretory pathway including protein folding, secretion, lipid synthesis, protein degradation, trafficking among other effects (Hetz et al., 2015). Alteration to the function of the ER and the secretory pathway are emerging as transversal and common drivers of neurodegeneration on a variety of pathological conditions affecting the nervous system (Hetz and Mollereau, 2014; Scheper and Hoozemans, 2015). In addition, the buffering capacity of the proteostasis network decays with aging, the main risk factor to develop neurodegenerative diseases (Mardones et al., 2015; Kaushik and Cuervo, 2015; Morimoto and Cuervo, 2014). However, functional studies using genetic or pharmacological manipulation of ER stress signaling have depicted a complex scenario where depending on the disease context and the UPR component analyzed disparate consequences are observed in terms of disease progression and histopathological changes. In this special issue of *Brain Research*, we provide a series of specialized reviews to discuss the current state of the field and provide examples about the impact of protein misfolding and aggregation to ER dysfunction, the causal role of ER stress in disorders of the CNS, in addition to possible therapeutic strategies to alleviate ER stress.

In this issue of *Brain Research* Lederkremer et al. provide general and in depth insights into the mechanisms associated with the development of ER stress upon protein aggregation, and accumulation in various NDs, and further explore possible therapeutic interventions targeting misfolded proteins and ER stress. Vidal et al. complement this review with a discussion about the role of ER chaperones in preventing neurodegeneration. Rebecca Taylor overviews novel concepts about the systemic control of ER proteostasis through cell-nonautonomous mechanisms. In addition a series of disease-oriented reviews are provided. Lin et al. deliver a comprehensive insight into the impact of ER stress and the UPR in degenerative diseases of the eye such as retinitis pigmentosa; arising from misfolded rhodopsins and achromatopsia caused by genetic mutations in Activating Transcription Factor 6 (*ATF6*) gene. Soto et al. provide an in depth review on Prion diseases and the cross-talk between ER stress signaling pathways and quality control systems which might be involved in regulating the degenerative. Mallucci et al. discuss approaches to boost memory and prevent synaptic loss in Alzheimer's disease and frontotemporal dementia and provide detailed insights into strategies to reverse the eIF2α mediated translational failure, which inhibits the expression of critical synaptic proteins. Mercado et al. focus on Parkinson disease (PD) and provide novel insights about PD

http://dx.doi.org/10.1016/j.brainres.2016.09.014

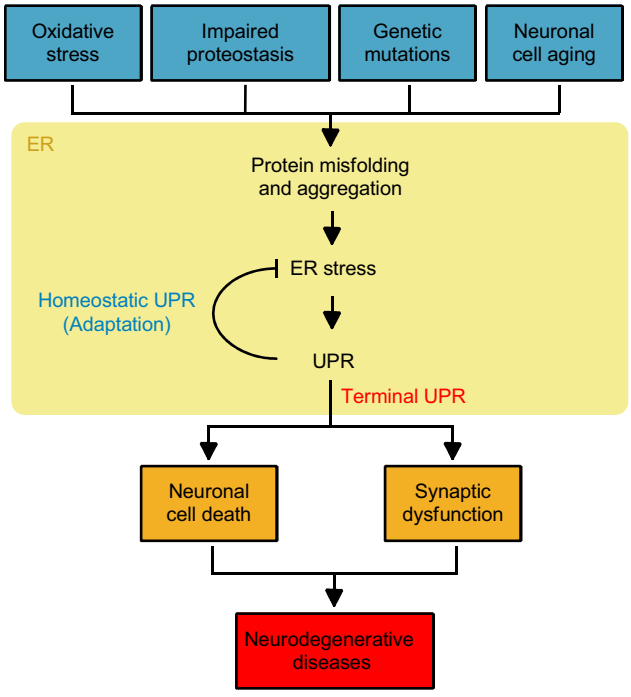

Fig. 1. ER stress and brain dysfunction. Model for the impact of endoplasmic reticulum (ER) stress in neurodegeneration and other pathological conditions affecting the nervous system.

pathogenesis and the contribution of secretory pathway disruptions to disease progression. Lajoie et al. present evidence linking Huntington's disease (HD) to ER stress and discuss strategies to modulate signaling pathways that diminish misfolded protein accumulation in the ER, thereby reducing toxicity and ER stress. Saxena et al. provide insights into the process of proteostasis and offer specific insights into how its impairment can lead to the degeneration of motoneurons in amyotrophic lateral sclerosis (ALS). Atkin et al. discuss the role of protein misfolding in impairing quality control mechanisms in ALS and highlight the role of chaperones in ALS, and their possible applications as therapeutic targets. In addition to neurodegenerative diseases, the UPR is also emerging as an important mediator of cell's dysfunction in pathological conditions triggered by injury to the nervous system through mechanical damage, autoimmunity, among other insults. Court et al. overview the emerging role of ER to injury to the CNS and peripheral nervous system including spinal cord injury, peripheral neuropathies and stroke. Brian Popko discusses the functional contribution of the UPR to myelin-mediated disorders including multiple sclerosis. Finally, Chevet et al. assess the emerging role of the UPR as a driver of brain cancer, discussing the functional link between UPR signaling and the hallmarks of cancer.

Different strategies to ameliorate ER stress are under development including pharmacological and gene therapy approaches. Here Bollereau et al. review an interesting novel concept where mild perturbations to the ER proteostasis network may generate a preconditioning condition that engages UPR adaptive programs. This concept is referred to as *ER Hormesis* and is currently exploited as a way to provide protection against neurodegeneration. Although increasing number of small molecules are available to target ER stress, the use of small molecules to treat chronic brain diseases is challenging because of poor blood brain barrier permeability and undesirable side effects due to known role of the UPR in the physiology of peripheral organs. Gene therapy is under development as an alternative to circumvent these problems by the delivery of adaptive UPR components to selective regions and cell types of the nervous system. Here Hetz et al. provide an overview about the state of the art on gene therapy efforts to reduce ER stress levels in brain diseases.

Sustaining the functionality of the neuronal proteome requires an efficient integration of the proteostasis network to support synaptic function, which is monitored on a dynamic way by the UPR. As discussed in this review series, increasing evidence indicates that ER stress contributes to neurodegeneration, where distinct UPR signaling branches may have specific downstream consequences on a variety of mechanistically unrelated pathological conditions including brain cancer, autoimmunity, injury to the nervous system and neurodegeneration. As discussed in this special issue, the current state of the field suggests that future therapeutic strategies to alleviate ER stress may translate into beneficial effects to alleviate neurodegeneration and improve brain function. Due to the fast development of pharmaceutical efforts to design ER stress targeting drugs, in the next few years it is expected to witness important translational efforts to test the real potential of ER stress to disease and the feasibility to target the pathway in clinical trials (Fig. 1).

Acknowledgments

Supported by Millennium Institute No. P09-015-F, and FONDAP 15150012, the Frick Foundation 20014-15, ALS Therapy Alliance 2014-F-059, Muscular Dystrophy Association 382453, CONICYT-USA 2013-0003, Michael J Fox Foundation for Parkinson´s Research – Target Validation grant No 9277, COPEC-UC Foundation 2013. R.40, Ecos-Conicyt C13S02, FONDECYT no. 1140549, Office of Naval Research-Global (ONR-G) N62909-16-1-2003 and ALSRP Therapeutic Idea Award AL150111 (Claudio Hetz). Supported by Synapsis Foundation, Stiftung UNISCIENTIA, Frick foundation for ALS research and Swiss National Science Foundation Professorship grant no. 128460 and 150756 (Smita Saxena).

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