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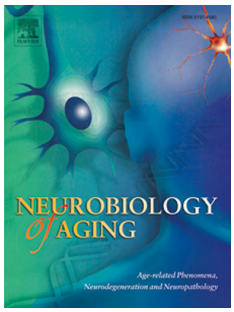

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Peer Commentary forum

A decay of the adaptive capacity of the Unfolded Protein Response exacerbates Alzheimer's disease

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Abstract

Alterations in the buffering capacity of the proteostasis network is a salient feature of Alzheimer's disease (AD), associated with the ocurrence of chronic endoplasmic reticulum (ER) stress. To cope with ER stress, cells activate the unfolded protein response (UPR), a signal transduction pathway that enforces adaptive programs through the induction of transcription factors such as XBP1. A new study by Marcora and coworkers used a fly model to study amyloid β pathogenesis in the secretory pathway of neurons. Through genetic manipulation, authors identified a new role of XBP1 in the clearance of amyloid β and the improvement of neuronal function. However, although the activation of the UPR signaling was sustained overtime, the transcriptional upregulation of XBP1-target genes was attenuated during aging. This study suggests that aging has a negative impact in the ability of the UPR to manage proteostasis alterations in AD.

Keywords: Alzheimer's disease, amyloid-β, unfolded protein response, XBP1, neurodegeneration, aging.

Main text

Neurodegenerative diseases are all characterized by the accumulation of protein aggregates in distinct brain areas. These diseases are now classified as protein-misfolding disorder (PMDs), and include Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and Alzheimer's disease (AD) among others (Soto, 2003). Emerging evidence in the field suggests that a reduction of the proteostasis network buffering capacity during aging may operate as a risk factor to undergo neurodegeneration (Hetz and Saxena, 2017; Kaushik and Cuervo, 2015). In the context of AD, amyloid β peptide and hyperphosphorylated Tau constitute the main protein lesions characterizing disease histopathology and are associated with the development of synaptic dysfunction, axonal degeneration and brain inflammation (Haass and Selkoe, 2007). One node of the proteostasis network that is drastically affected in AD involves impairment in the folding capacity of the endoplasmic reticulum (ER). In fact, ER stress is a common feature of AD as reported in patient derived post-mortem brain tissue and various animals and cellular models of the disease (Cornejo and Hetz, 2013; Scheper and Hoozemans, 2015; Smith and Mallucci, 2016). ER stress was also suggested to be a major pathological signature in human stem cell derived-neurons from AD patients (Kondo et al., 2013). Altogether, these studies delineate a paradigm where proteostasis

defects and abnormal protein accumulation during aging lead to neuronal dysfunction and synaptic impairment, a process exacerbated in AD. In a recent issue of *Neurobiology of Aging*, Marcora *et al*. studied the activation of ER stress sensors in a fly model of amyloid β toxicity and explored the relationship between proteostasis dysfunction and aging (Marcora et al., 2017). Overall, this study provides evidence indicating that the loss of an efficient proteostasis control may worsen the toxic effects of amyloid β deposition and that the UPR, the main signaling pathway engaged by ER stress, could play an important role in this regard.

The maintenance of proteostasis relies on a sensitive and constant monitoring of fluctuations in proteome integrity to avoid proteotoxicity due to the accumulation of abnormal protein aggregates. The proteostasis network represents a dynamic integration of biological pathways that control the biogenesis, folding, trafficking and degradation of proteins (Balch et al., 2008). Brain aging is characterized by various cellular and molecular alterations impacting proteostasis balance, including the generation of oxidative stress, dysfunctional autophagy and proteasomal impairment. (Kaushik and Cuervo, 2015). Most of these features are found exacerbated in the AD brain, which may result in ER stress. Three different ER stress sensors mediate the activation of the UPR, known as activating transcription factor 6) (ATF6), protein kinase RNA-like ER kinase (PERK) and inositol-requiring protein 1 (IRE1) (Walter and Ron, 2011). These stress transducers drive a global adaptive response to restore homeostasis or engage cell death programs in damaged cells (Hetz et al., 2015). Activation of ATF6 enforces the transcription of chaperone and ER-associated degradation (ERAD) genes. PERK phosphorylates the eukaryotic initiation factor-2α (eIF2α), leading to a global inhibition of protein synthesis. EIF2α phosphorylation allows the expression of the transcription factor ATF4, which controls the induction of genes involved in protein folding, the antioxidant response, autophagy and apoptosis (Wang and Kaufman, 2016). IRE1α catalyzes the unconventional splicing of the mRNA encoding a transcription factor known as X-box binding protein 1 (XBP1), a central player of the UPR promoting cell survival through an increase of folding capacity and degradation of misfolded proteins (Hetz, 2012). However, under sustained ER stress, IRE1α may trigger apoptosis by activating JNK or by directly degrading a subset of mRNAs through a process termed regulated IRE1 independent decay (RIDD) (Maurel et al., 2014). In the context of experimental AD, UPR activation has been involved in distinct aspects of the pathology, including cell survival, stress resistance, synaptic dysfunction and amyloid β deposition **(Figure 1)** (Cornejo and Hetz, 2013; Scheper and Hoozemans, 2015; Smith and Mallucci, 2016). However, the possible relationship between ER stress and aging, the main risk factor to develop AD, has not been explored.

The involvement of UPR signaling in AD pathogenesis is quite complex and the global picture of its functional role is still incomplete. For example, XBP1s overexpression in mouse models of AD is neuroprotective and associated with an improvement of synaptic plasticity (Cissé et al., 2016). This study is in agreement with a previous report indicating that XBP1s has an alternative function in the brain by controlling basal neuronal physiology, impacting learning and memory (Martínez et al., 2016). Conversely, PERK signaling has been shown to negatively impact synaptic plasticity in mouse models of AD through an inhibition of protein synthesis (Ma et al., 2013). This is consistent with the fact that eIF2α phosphorylation has a pivotal role in storing information in the brain (Costa-Mattioli et al., 2007). In addition, ATF4 expression locally in axons of AD mice propagates degenerative signals on a cell-nonautonomous manner (Baleriola et al., 2014). Furthermore, IRE1α was also recently identified as a contributor to neurodegeneration in an animal model of AD, where the genetic ablation of its RNAse domain led to a decrease of amyloid β levels in the brain and a reversion of the cognitive deficits (Duran-Aniotz et al., 2017). These unexpected results may be related to altered RIDD, raising the question about the balance between XBP1-dependent and -independent signaling events initiated by IRE1α.

Accumulating studies suggest that a decrease in the capacity to maintain normal proteostasis is one of the fundamental pillars of aging (Kennedy et al., 2014; López-Otín et al., 2013), highlighting the occurrence of ER disturbance as a central alteration (Martínez et al., 2017). Using a fly model of amyloid β toxicity, Marcora *et al* showed that aging exacerbates the deleterious effects of amyloid β accumulation, correlating with the development of behavioral alterations. Moreover, signs of UPR activation were reported on this model since the early stages of the disease and were maintained over time. Using functional approaches to define the significance of the UPR in this context, they confirmed the predicted finding that XBP1 deficiency accelerates disease progression and the accumulation of amyloid β, whereas down-regulating PERK in the same model was protective. However, the authors also reported an unexpected decrease in the expression of endogenous XBP1s transcriptional targets involved in the ERAD machinery when aged flies where analyzed. This reduced levels of UPR target genes occurred even when XBP1s was still activated by amyloid β accumulation and was correlated to the appearance of poly-ubiquitinated proteins and an impaired climbing behavior of the fly. Interestingly, the activity and stability of XBP1s in other systems is modulated by post-translational modifications such as sumoylations, acetylations or phosphorylation, in addition to epigenetic changes and genetic backgrounds (Hetz et al., 2015). However, the possible mechanisms underlying the attenuation of XBP1-dependent responses in AD flies remain to be established. Taken together, these findings suggest that aging impairs specific adaptive UPR responses, which may enhance the detrimental effects of PERK overactivation in

experimental AD.

Overall, the current studies added a new layer of complexity to the field by exploring the contribution of aging to ER stress and AD pathogenesis. The results provided by Marcora and colleagues suggest that strategies to enforce the prosurvival outputs of the UPR in brain diseases may be inefficient during aging. However, this hypothesis remains to be explored in mammals. In addition, most data relating ER stress with brain aging in mammals relies on correlative observations while functional studies to address this major question are still missing (Martínez et al., 2017). On the other hand, accumulating evidences indicate that overexpression of UPR components in various in vivo models can reverse or protect against features of experimental AD. For example, studies using the fly eye as a model system, demonstrated that enforcing the expression of XBP1s is protective against amyloid β and Tau toxicity (Casas-Tinto et al., 2011; Loewen and Feany, 2010). In agreement with these findings, a recent report successfully delivered XBP1s into the brain using recombinant viruses and reversed the cognitive deficits of a transgenic mouse model of AD (Cissé et al., 2016). Similar strategies have been employed with positive results in various pre-clinical mouse models of neurodegenerative diseases, indicating that UPR modulation represents a promising target for future therapeutic interventions (Hetz and Saxena, 2017). However, little is known about the efficacy of theses approaches in the context of an aged animal. Because one of the limitations of transgenic models is the relatively early and massive accumulation of the disease-related protein, it has not been possible to assess the actual impact of aging on any external intervention aiming at reduce ER stress levels. Additionally, fundamental knowledge is lacking about how altered proteostasis during aging can modify amyloid β metabolism and Tau aggregation and its actual relation to synaptic dysfunction. Overall, accumulating evidences is starting to delineate the importance of proteostasis dysfunction during brain aging and neurodegenerative condition such as AD. However, most of the data available were generated by the use of simple model organisms such as *C. elegans* or *D. melagonaster* and functional studies in disease models that are closer to humans are still needed. The work presented by Marcora and colleagues sets the basis of an interesting proof-of-concept linking ER stress and aging in AD and encourage the development of new studies to elucidate the involvement of proteostasis impairment in aged mammals and brain diseases. Such approaches are predicted to provide important insights about the transition between normal aging and disease states related to protein misfolding. Since aging is the major risk factor to develop most neurodegenerative diseases, it is becoming clear that this central factor needs to be considered in future efforts to define pathological mechanisms and novel therapeutic strategies.

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Competing Interests

The authors declare that they have no competing interests.

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Legend

Figure 1: Involvement of ER stress in AD. AD is characterized by the presence of aggregated proteins and synaptic dysfunction. Accumulating evidence indicates that proteostasis alterations are a hallmark of the disease, highlighting the occurrence of endoplasmic reticulum (ER) stress. Activation of the unfolded protein response (UPR) engages adaptive programs to recover ER proteostasis. However, under chronic ER stress, the UPR switches it signaling toward a cell death response (terminal UPR). In the context of AD, these different UPR outputs are described: (i) the expression of the UPR transcription factor XBP1s enhances the cognitive capacity of the brain and

also (ii) induces target gene involved in ER stress mitigation, whereas PERK signaling triggers (iii) synaptic impairment and neurodegeneration. Aging may alter the ability of the adaptive phase of the UPR to recover proteostasis through XBP1s, which may in turn enhance the deleterious effects of PERK in AD.