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Review

ER stress and Parkinson's disease: Pathological inputs that converge into the secretory pathway

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ABSTRACT

The major clinical feature of Parkinson's disease (PD) is impairment in motor control as a result of extensive dopaminergic neuron loss in the substantia nigra pars compacta. The central pathological hallmark of PD is the formation of neuronal cytoplasmic inclusions of insoluble proteins called Lewy bodies, of which fibrillar aggregates of misfolded αSynuclein are the major components. Despite intense research on the pathogenic mechanism that trigger neuronal loss and disease progression, the neurogenesis of PD remains unknown. However, studies on genetics of PD have identified specific genes and proteins linked to this disease. Genetic mutations linked with different forms of familial PD have unveiled a closer relationship between pathology and impairments at different points in the secretory pathway. Accumulation of misfolded/unfolded proteins in the endoplasmic reticulum and disruptions in protein clearance mechanisms result in activation of an adaptive stress pathway known as the unfolded protein response (UPR). UPR signaling is mediated by three stress sensors that induce independent and convergent signaling branches that help to maintain homeostasis, or eventually trigger cell death under chronic stress conditions. Signs of ER stress are observed in post-mortem tissue from sporadic human PD cases and in most animal models of the disease, implicating all three branches of this cellular response. However, the exact contribution of the UPR in the progression of PD or in dopaminergic neuron survival is not yet well understood. A large number of studies reveal a clear activation of the UPR in toxicological models resembling sporadic PD, where ATF6, XBP1 and CHOP have a functional role in controlling dopaminergic neuron survival in neurotoxin-based models of PD *in vivo*. Also pharmacological and gene therapy approaches aimed to target different points of this pathway have revealed an important functional role in PD pathogenesis.

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Abbreviations: PD, Parkinson's disease; SNpc, substantia nigra pars compacta; LB, Lewy bodies; αSyn, αSynuclein; ER, endoplasmic reticulum; ERAD, ER-Associated Degradation; PINK1, PTEN-induced putative kinase 1; ATP13A2, lysosomal P-type transport ATPase; LRRK2, leucine-rich repeat kinase 2; VPS35, vacuolar protein sorting-35 protein; UCHL-1, ubiquitin carboxy-terminal hydrolase L1; GCase, β-glucocerebrosidase; DAT, dopamine transporter; SNARE, soluble NSF attachment protein receptor; TFEB, transcription factor EB; CHIP, C-terminus of Hsp70-interacting protein; Pael-R, parkin-associated endothelin receptor-like receptor; UPR, unfolded protein response; IRE1α, RNA-activated protein inositol requiring kinase 1α; ATF6, activating transcription factor 6; PERK, kinase-like ER kinase; BiP, Glucose regulated protein 78 (Grp78); XBP1, transcription factor X-Box binding protein 1; eIF2α, eukaryotic initiation factor 2α; GADD34, growth arrest and DNA damage-inducible protein 34; CHOP, C/EBP homologous protein; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine; AAV, adeno-associated viral vectors

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and affects about 1% of the elderly population. A known risk factor for PD is age, suggesting that its prevalence is likely to increase in the next several years. PD is a progressive neurodegenerative disease that impairs movement control, and is often accompanied by dementia. PD is pathologically characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and by the presence of intraneuronal inclusions, termed Lewy bodies (LB), where fibrillar aggregates of αSynuclein (αSyn) constitute a major component (Spillantini et al., 1997).

As in all neurodegenerative diseases, PD represent a major challenge in terms of a large and rapidly increasing population that is afflicted and the lack of effective treatments. The ultimate objective for a disease-modifying therapy is to slow down or even stop disease progression. To accomplish this goal, research focused on genetics and pathophysiology of the disease is fundamental to understand the process of dysfunction and degeneration.

A major focus of study in the field is the understanding of the mechanisms involved in the selective neuronal vulnerability of dopaminergic neurons in PD. Recent accumulating evidence supports the concept that disruptions in the secretory pathway function is an important contributor to the pathogenic processes, ultimately leading to aggregated protein accumulation and dopaminergic neuron loss in PD.

2. Secretory pathway dysfunctions and PD

Genetic mutations linked to different forms of familial PD have unveiled a closer relationship between pathology and different points in the secretory pathway (Fig. 1). The secretory pathway is not only composed of the endoplasmic reticulum (ER) and Golgi compartments but is formed by the entire biosynthetic-secretory and endocytic pathways. In these pathways, proteins and other cellular components are transported by a complex network of vesicular compartments that fission and fuse from the ER to Golgi to the cell exterior and back to early endosomes and lysosomes via recycling pathways, and even back to the ER. Recently, the generation of neuronal cultures from induced pluripotent stem cells derived from PD patients, indicated that ER stress leads to accumulation of ER-Associated Degradation (ERAD) substrates and that ER stress is a salient molecular signature of the disease (Chung et al., 2013).

Causes of PD are mostly sporadic with no or not yet identified genetic cause(s), and it is estimated that only 5–10% of patients exhibit monogenic forms of the disease (Lesage and Brice, 2009). Some of the identified genes involved in autosomal recessive PD are the ones that codified for the ubiquitin E3 ligase, Parkin, PTEN-induced putative kinase 1, (PINK1), protein deglycase DJ-1, and the lysosomal P-type transport ATPase (ATP13A2). Genes involved in autosomal dominant PD are SNCA locus that encode αSyn protein, leucine-rich repeat kinase 2 (LRRK2), vacuolar protein sorting-35 (VPS35), and ubiquitin carboxy-terminal hydrolase L1 (UCHL-1) (Klein and Westenberger, 2012). In addition, genome-wide association studies found that LRRK2, αSyn, β-glucocerebrosidase (GCase) and dopamine transporter (DAT), are common risk factors for sporadic PD (Mullin and Schapira, 2015).

Mutations within αSyn as well as duplication and triplication of the SNCA locus, result in an acceleration of pathogenic aggregation of this protein and neurodegeneration (Conway et al., 2000; Chartier-Harlin et al., 2004; Choi et al., 2004; Kruger et al., 1998; Polymeropoulos et al., 1997; Zarranz et al., 2004). αSyn is predominately a presynaptic terminal protein and despite its relevant role in the pathophysiology of PD, the physiological function and the molecular pathways mediating αSyn neurotoxicity remains unsolved. It has been described that the physiological function of the protein would be chaperone soluble NSF attachment protein receptor (SNARE) complex assembly at the synapse (reviewed in Burre (2015)). In contrast, its pathological function would be related to its misfolded conformation leading to neurotoxic aggregates that are characteristic of the disease. Homozygous SNCA knockout mice do not display any PD phenotype, although there are some reports of mild impairment in vesicle trafficking and dopamine release (Abeliovich et al., 2000; Cabin et al., 2002; Chandra et al., 2004).

Cellular studies show a functional relationship between αSyn and Rab1 in yeast, and Rab3a in mammalian cells, where impairment of vesicle exit from the ER triggers the accumulation of immature proteins from this compartment (Cooper et al., 2006; Thayanidhi et al., 2010). Overexpression of Rab1 rescues dopaminergic neuron loss induced by αSyn overexpression. Additionally, more recent studies in the field indicate that overexpression of mutant αSyn triggers chronic ER stress, inducing cell death, possibly due to a block in ER to Golgi vesicular trafficking of ATF6 (Credle et al., 2015).

Under physiological conditions, αSyn is usually degraded by the autophagy–lysosome system including chaperon-mediated autophagy and the ubiquitin-proteasome system (reviewed in da Fonseca et al. (2015)). In pathological conditions, αSyn can impair all these degradation pathways, and furthermore, disturbances in the autophagy-lysosomal system can contribute to its toxicity and accumulation in the cell, triggering ER stress (Chu et al., 2009; Decressac and Bjorklund, 2013; Winslow et al., 2010). Additional evidence that autophagy increase clearance of αSyn and LB came from *in vivo* studies, where treatments with the autophagy inducer trehalose reduce aggregate αSyn levels in mice and rats (He et al., 2015; Tanji et al., 2015), and even improve motor performance in a rat model of PD (He et al., 2015).

In this regard, it has recently been shown that αSyn-mediated toxicity in nigral dopaminergic neurons is accompanied by the cytosolic retention of transcription factor EB (TFEB), a major transcriptional factor of the autophagy-lysosomal pathway, possibly by a direct protein:protein interaction (Decressac et al., 2013). Moreover, *in vivo* manipulation of TFEB levels can modify αSyn-mediated toxicity (Decressac et al., 2013). In cellular models, it has been described that TFEB can translocate to the nucleus in response to ER stress (Martina et al., 2016).

One of the recently described PD genes encodes for the vacuolar protein sorting-35 (VPS35) protein of the retromer complex that plays an essential role in endosome-to-Golgi retrieval of membrane proteins. A D620N mutation in the VPS35 gene has been identified in patients with autosomal dominant PD (Vilarino-Guell et al., 2011). Dysfunction of this gene in Drosophila models increased αSyn accumulation in lysosomes and impaired locomotion (Miura et al., 2014). VPS35-deficient mice exhibited PD-relevant deficits including accumulation of αSyn in nigral dopaminergic neurons,