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α-Synuclein, and the Case of the Blocked ER-Golgi Pathway

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Summary

Parkinson’s disease has long been associated with Lewy Bodies composed of the protein α-synuclein. A groundbreaking new study has demonstrated the pathological function of α-synuclein may be impairment of ER-Golgi traffic.

Introduction

Parkinson’s disease (PD) is a fatal neurodegenerative disorder of the brain. It affects 1 in 100 individuals over the age of 60 of which 5-10% of cases occur in individuals under 40, and another ~5-10% are familial (NPF, 2006). PD is the result of neuronal atrophy within the substantia nigra located in the brain stem. The substantia nigra is part of a complex circuit called the basal ganglia. It is responsible for the initiation of movement (Purves et al., 2004). The hallmark feature of PD is neurofibrillary inclusions, Lewy Bodies, composed primarily of the protein α-synuclein (αSyn; Spillantini et al., 1998). Familial forms of PD have been linked to the αSyn mutations A30P (Krueger et al., 1998), A53T (Polymeropoulos et al., 1997), and recently E46K (Zarranz et al., 2004). However, the reason these cells are dying in PD patients remains unknown even after more than a decade of heavily funded research!

αSyn’s pathological component has often been associated with its role in Lewy Bodies. One widely accepted hypothesis is that αSyn is pathological when in a protofilibrillar form that occurs between monomeric αSyn disappearance and Lewy Body appearance (Lansbury et al., 2003). However, a remarkable new manuscript, “α-Synuclein Blocks ER-Golgi Traffic and Rab1 Rescues Neuron Loss in Parkinson’s Models”, by Lindquist et al. (2006) has demonstrated that the pathogenicity of αSyn may be due to the impairment of ER-Golgi traffic, resulting in a halt of critical cellular secretory processes.

Prior to their research, little was known about α-Syn’s relationship with the ER-Golgi pathway. However, αSyn expression led to the fragmentation of the Golgi apparatus (Fujita et al., 2006 and Gosavi et al., 2002). Notably, Gosavi et al. (2002) found Golgi fragmentation to occur before Lewy Body formation but after the disappearance of monomeric αSyn. Contrary to the αSyn-Golgi interaction, Lee et al. (2005) revealed αSyn to be excreted from the cell via a vesicular, ER-Golgi independent, exocytotic pathway. Thus, debate exists over which pathway αSyn is involved in.

The Case of the Blocked ER-Golgi Pathway

In the recent Lindquist et al. (2006) study, they wanted to determine the effect of αSyn on the ER-Golgi pathway. In order to accomplish this task, they took two approaches; one genetic and the other cellular. Together these different pathways would converge to implicate αSyn in the blocking of ER-Golgi traffic and cell death.

αSyn was expressed in yeast and regulated with a galactose inducible promoter. After αSyn expression, ER stress was measured and found to be increased for cells expressing αSyn-WT and further increased for the familial mutant αSyn-AS3T. Lindquist et al. (2006) hypothesized that αSyn was causing ER stress by blocking the function of endoplasmic reticulum associated degradation (ERAD). As misfolded proteins accumulate in the ER, the ERAD process functions by retrotranslocating them back into the cytoplasm for proteasomal degradation (McCracken and Bodsky 2006). They found that out of two commonly misfolded proteins in the ER, CPY and Sec61p2p (both ERAD substrates), the rate of CPY degradation decreased even though proteasomal function was unaltered. Interestingly, Caldwell et al. (2001) demonstrated that ERAD degradation of CPY required transport through the Golgi.

Because the failure of the ERAD translocation through the ER to the Golgi during αSyn expression may be an indicator of general pathway blockage, Lindquist et al. (2006) hypothesized that αSyn may be blocking ER-Golgi traffic. To determine if this was the case, they followed two proteins, CPY and ALP, through the ER-Golgi circuit when αSyn was expressed. Within three hours, ER-Golgi traffic was greatly reduced and at four hours nearly nonexistent. Simultaneously, cell growth inhibition also occurred. Thus, αSyn blocks ER-Golgi traffic (2006).

Following their cellular approach, Lindquist et al. (2006) initiated a genetics approach aimed at determining if genes that enhance ER-Golgi transport could reduce αSyn’s ability to block the pathway. They identified the yeast protein Ypt1p as a promoter of traffic, and Gyp8P as a suppresser of traffic. This finding led Lindquist et al. (2006) to hypothesize that over-expression of the Ypt1p (yeast) or Rab1 (mammalian) in a variety of models would rescue them from αSyn toxicity.

This final study yielded profound results that provided the strongest evidence, yet, that αSyn’s impairment of ER-Golgi traffic was the source for toxicity. They overexpressed Rab1 along with αSyn in Drosophila melanogaster (fruit fly), C. elegans (worm), and mammalian dopaminergic neurons to determine if Rab1 would prevent αSyn toxicity by enhancing ER-Golgi traffic. In all three models, the cells were rescued from death when overexpressing Rab1.

As a result of Ypt1p/Rab1 re-establishing ER-Golgi traffic, it was hypothesized that αSyn interacted at the ER-Golgi junction. This was based on two lines of evidence; 1) CSP requires transport into the Golgi to be degraded and 2) Ypt1p/Rab1 functions within the ER-Golgi vesicular binding pathway. Therefore, when Ypt1P/Rab1 is over-expressed, vesicular binding efficiency increases.

Returning to the Gosavi et al. (2002) and Lee et al. (2005) manuscripts, the Lindquist et al. (2006) data provides two established lines of evidence (i.e. detailed previously) supporting the Gosavi et al. (2002)
conclusion that αSyn interacts with the ER-Golgi to yield toxicity. Though αSyn is continuously being secreted through a Golgi-ER independent pathway (Lee et al., 2005), it is plausible that a defect in this excretory system may function to exacerbate toxicity, but not produce it.

Future Research

The Lindquist et al. (2006) manuscript has provided the Parkinson’s disease community with what appears to be an opened door, leading to a whole new frontier in PD research and understanding. As with the relentless pursuit of the protofibrillar discovery by Dr. Lansbury, all methods of research must be exhausted on finding the mechanism by which αSyn is able to turn off the ER-Golgi pathway. It is feasible that the same lentivirus used by Lindquist et al. (2006) to carry the Rab1 gene into mammalian neurons in their experiments could be re-configured to enter the cells of PD patients and re-establish traffic between the ER and Golgi. If this is, in fact, the reason these cells are dying, one of the most prevalent and debilitating neurodegenerative diseases could be cured.

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