Symposium 9
Parkinson Disease Genes, Protein Degradation and Mitochondrial Quality Control

S09-01

ENDOPLASMIC RETICULUM STRESS IS ASSOCIATED WITH α-SYNUCLEINOPATHY IN TRANSGENIC MOUSE MODEL

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Accumulation of aggregated α-synuclein (αS) is a pathological hallmark of Parkinson's disease (PD) and other α-synucleinopathies. Cellular accumulation of misfolded proteins is often associated with activation of endoplasmic reticulum (ER) stress pathway or unfolded protein response (UPR). Recent studies implicate ER stress in αS toxicity in cellular context. Herein, we show that transgenic (Tg) mice overexpressing mutant human (Hu) αS exhibits ER stress with onset of neurodegeneration. With the disease A53T HuαS Tg mice exhibit increased levels of ER chaperons (BIP/Grp78, Grp94 and PDI) and activation of ER stress-related transcription factors, ATF6 and xbp1. However, induction of ER chaperons occurred in absence of the expected increase in the phosphorylation of eIF2α. This abnormal ER-stress response the A53T HuαS Tg mice was associated with increased levels of cleaved caspase 12, an ER stress-related caspase in mouse, and increased activation of caspase 9, a downstream target of cleaved caspase 12. The above signs of UPR coincide with disease and were not seen in areas that are not affected by α-synucleinopathy (e.g. Cortex). Thus, the ER stress and activation of caspase 12 and 9 are selectively associated with α-synucleinopathy.

Analysis of microsomal fractionations from spinal cords of A53T HuαS Tg mice shows that αS is associated with the ER/microsome fraction and the levels microsomal αS increases with onset of disease and induction of ER stress. In addition to the monomeric αS in the lumen of microsomes, oligomeric αS are associated with outside of microsomes. Co-immunoprecipitation and cross-linking studies show that ER chaperones are associated with microsomal αS. Analysis of human PD cases show increased microsomal αS in PD cases. We hypothesize that accumulation of misfolded/aggregated αS in the ER of A53T HuαS Tg mice causes ER-stress. abnormal UPR, and contributes to neurodegeneration.

Supported by NIH Grants NS38065 and NS38377.

S09-02

PARKIN-MEDIATED UBIQUITINATION AND REGULATION OF SYNAPTIC PROTEINS

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Mutations in the Parkin gene cause an autosomal recessive juvenile-onset form of PD that account for a large fraction of familial cases. It is now well established that the parkin protein functions as an E3 ubiquitin (Ub)-ligase. Ubiquitination targets substrates to different cellular pathways depending on the length and architecture of the Ub chain. Typically, substrates modified with lysine 48 (K48) linked Ub chains are targeted to the proteasome for degradation, whereas substrates modified with Ub chains linked via K63 or mono-Ub influence cellular functions as diverse as signal transduction, transcription and membrane trafficking. In addition to assembling canonical K48-linked Ub chains, parkin has been shown, under certain circumstances, to assemble K63-linked Ub chains as well as the attachment of mono- and multi-mono-Ub, implicating it in proteasome-independent pathways. In particular, we have shown that parkin regulates cell-surface receptor trafficking and kinase signaling pathways via the mono-ubiquitination of adaptor proteins such as Eps15 and PICK1. More recently, we have been exploring the role of the N-terminal parkin Ub-like (Ubl) domain as a versatile interaction module, connecting parkin to proteins involved in ubiquitination and trafficking. In addition to the well-characterized Ub-Interacting Motif (UIM), we have identified the SH3 domain within proteins such as endophilin-A as a novel parkin Ubl-interacting module. The structural basis and functional consequences of the interactions will be discussed along with an attempt to link the findings to pathways relevant to neurodegeneration, including mitochondrial quality control.

S09-03

PARKINSON'S DISEASE: PINK1 AND MITOCHONDRIAL COMPLEX I FUNCTION

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The etiology of PD remains unknown, although clinical and experimental evidence implicate the involvement of mitochondrial dysfunction and oxidative stress. Exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or to rotenone, both Complex I toxins, caused parkinsonism in humans and in laboratory animals. Mutations in the mitochondrial kinase PINK1 cause recessive inherited early onset PD. Overexpression and loss of function studies have implicated PINK1 in apoptosis, abnormal mitochondrial morphology, impaired dopamine release and motor deficits. However, the underlying molecular mechanisms remain to be clarified. Using Drosophila and mouse models we show here that PINK1 deficiency or clinical mutations impact on the function of Complex I of the mitochondrial respiratory chain, resulting in mitochondrial depolarization and increased sensitivity to apoptotic stress in mammalian cells and tissues. In neurons we find that Pink1 deficiency affects synaptic function in Drosophila neurons as reserve pool of synaptic vesicles is not mobilized during rapid stimulation. The fundamental importance of Pink1 for energy maintenance under increased demand is further corroborated as this deficit can be rescued by adding ATP to the synapse. The clinical relevance of our