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Mechanism and prevention of tau oligomer toxicity in alzheimer's disease

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Alzheimer's disease (AD) is characterized by the accumulation of intracellular neurofibrillary tangles (NFTs) composed of insoluble aggregates of the microtubule-associated protein tau. Tau aggregates have been hypothesized to cause neurotoxicity based on the spaciotemporal correlation of NFTs with cognitive decline. Though the precise mechanism of neurotoxicity remains to be elucidated, one potential mechanism is via the disruption of microtubule-dependent axonal transport. Current evidence indicates that neuronal dysfunction actually precedes the formation of insoluble NFTs, suggesting that prefibrillar aggregates may in fact be the toxic species. Recent work from the Binder and Brady laboratories focuses on characterizing prefibrillar tau aggregates as well as strategies to prevent their toxicity. Using a tau oligomer selective antibody, we demonstrate that prefibrillar tau oligomers are present in markedly elevated quantities in AD and that these aggregates precede the formation of AD pathology. Using the squid axoplasm model, we provide compelling evidence that inhibition of anterograde fast axoplasmic transport is a mechanism of tau oligomer-mediated toxicity. This inhibition is likely caused by a conformational change occurring in tau oligomers that results in the exposure of the phosphatase activation domain (PAD) of tau located at the extreme N-terminus. Our collective laboratories have demonstrated that the aberrant exposure of PAD results in the activation of a GSK-3 mediated pathway that causes kinesin to release its cargo. Interestingly, the molecular chaperone Hsp70 can preferentially bind tau oligomers to prevent this inhibition of transport. Thus, modulation of molecular chaperones provides a potential mechanism for the prevention of tau oligomer-mediated toxicity.

Biography

Kristina Patterson completed her Ph.D in Cell and Molecular Biology at Northwestern University in 2011. She is currently working on the completion of her MD at Northwestern University's Feinberg School of Medicine.

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