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Can tau pathobiology be phenocopied in a cellular expression model?

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Tau hyperphosphorylation and formation of insoluble tau deposits are principal aspects of the neurofibrillary pathology associated with Alzheimer's disease (AD) and other neurodegenerative tauopathies. Despite a histology-based focus on insoluble filamentous tau pathology, small soluble tau oligomers have recently been implicated in the promotion of neurodegenerative activities and are now widely viewed as central participants in disease-related neurodegeneration. The factors that initiate the aberrant post-translational processing of tau and the generation of toxic tau oligomers are not well defined, but hyperphosphorylation has been implicated to play a critical role in tau aggregation. We have generated a cellular model in which full length human tau is expressed as a dimer-like structure that we refer to as tandem repeat tau (TRT). Cellular expression of TRT results in rapid hyperphosphorylation of the protein at disease-relevant epitopes. The rapid hyperphosphorylation is followed by a slower formation of high molecular weight tau oligomers that are stable to detergent extraction and gel filtration. TRT displays proteolytic processing with multiple cleavage products that are not observed for the monomeric version of tau. Cells expressing TRT show increased propensity for caspase activation and an activation of the unfolded protein response, suggesting that TRT expression initiates a cascade of pathological cellular responses that compromise cellular viability. Given multiple observations of similar post-translational processing of TRT in this model, compared to tau pathology in brains of patients with AD and other neurodegenerative tauopathies, we suggest that this model may be useful for delineating cell biology associated with tauopathy, as well as providing a model system for testing potential therapeutic agents.

Biography

Joel B Schachter is currently a Principal Scientist in the Movement Disorders and Translation Group at Merck. He joined Merck in 2009 as Director of Neurology and has held several positions there including Head of External Discovery and Preclinical Sciences for Neuroscience (XDPS) and Franchise Collaboration Lead for Neuroscience. In his role within XDPS, he was involved in building effective collaborations with external partners and in execution of preclinical drug discovery programs in the areas of Alzheimer's disease, Parkinson's disease, schizophrenia, and pain/migraine. As Franchise Collaboration Lead, he developed collaborative basic research efforts with academic partners. Prior to his work at Merck, he has spent 12 years at Pfizer as a Member of the Molecular Sciences Department and the Neurology group where he led project teams for several Alzheimer's Disease-related drug discovery programs including GSK3, gamma modulators, and tau new targets.

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