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Therapeutic approaches to prevent the spreading of tauopathy in Alzheimer's disease

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Abnormal folding of tau protein leads to the generation of paired helical filaments (PHFs) and neurofibrillary tangles, a key neuropathological feature in Alzheimer's disease (AD) and tauopathies. The specific anatomical pattern of pathological changes developing in the brain suggests that once tau pathology is initiated, it propagates between neighboring neuronal cells, possibly spreading along axonal networks. In other words, misfolded aggregated tau protein released by degenerating neurons can mediate and spread toxicity to neighboring cells. We studied whether PHFs could be taken up by cells and promote the spreading of tau pathology. Neuronal and non-neuronal cells overexpressing green-fluorescent protein tagged tau (GFP-Tau) were treated with isolated fractions of human AD-derived PHFs for 24h. We found that cells internalized PHFs through an endocytic mechanism and developed intracellular GFP-Tau aggregates with attributes of aggresomes. This was made particularly evident by the perinuclear localization of aggregates and the re-distribution of vimentin intermediate filament networks and retrograde motor protein dynein. Furthermore, the content of Sarcosylinsoluble tau, a measure of abnormal tau aggregation, increased 3-fold in PHF-treated cells. Exosome related mechanisms did not appear to be involved in the release of GFP-Tau from untreated cells. Collectively, paired helical filaments can mediate the spreading of pathological tau aggregation. Paired helical filament-mediated formation of aggresome-like bodies may be important in neurodegeneration. The evidence that cells can internalize PHFs leading to the formation of aggresome-like bodies opens new therapeutic avenues to prevent the propagation and spreading of tau pathology.

Biography

Dr. Giulio Maria Pasinetti's research on lifestyle factors and metabolic co-morbidities influencing clinical dementia, neurodegeneration and Alzheimer's disease has made him a top expert in his field. He has received over 30 grants and published over 160 groundbreaking research articles. Dr. Pasinetti is a Professor of Neurology, Psychiatry, Neuroscience, and Geriatrics and Adult Development, and is Director of the Brain Institute Center of Excellence for Novel Approaches to Neurotherapeutics at Mount Sinai School of Medicine. He also serves as Director of the Basic and Biomedical Research and Training, Geriatric Education and Clinical Center at the Bronx Veterans Affairs Medical Center.

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