Flow Cytometry Distinguishes Synaptosome Populations Containing a Progression of AD Pathologic Markers in Human Autopsy Brain and Tg Animal Model

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Abstracts will be considered for both poster and platform presentations

Other neurodegenerative disorders

One of the impediments to developing disease-modifying therapeutics for Alzheimer's disease (AD) is that current animal models do not fully recapitulate the pathological details or the severity of the cognitive dysfunction of the human disease.
Two differences between AD in humans and animal models of AD are: 1) in humans, AD Aβ amyloid pathology binds the imaging ligand, Pittsburgh Compound B (PIB), and 2) in humans, tau pathology develops along with severe cognitive symptoms.
In animal models of AD the Aβ pathology binds a minimal amount of PIB, and neither tau pathology nor severe cognitive symptoms develop. We found that isolated synaptic endings (synaptosomes) from human AD brain bind much more 3H-PIB than synaptosomes from non-cognitively impaired (NCI) human brain. This suggested that this synaptic, non-plaque PIB binding could be a marker for an early step in a progression of pathologic events that begins in the synapse. We hypothesize that in animal models either some component for the disease process to advance is missing or that the models somehow successfully reverse or block the pathological changes.
In order to detect affected synapses at early stages of the disease, we applied flow cytometry to analyze individual synaptosomes isolated from human frontal cortex of a series of autopsy cases. Complement C1q marks damaged synaptic endings, but additional processes are required to trigger pruning of the synapse. We find that in PSD95+ particles (defined as synaptosomes) in a given NCI human brain, a proportion of synaptosomes contain C1q, as well as Aβ, and fluorescent CN-PIB in a pattern that suggests a sequential process. The proportion of affected synaptosomes in an NCI brain increases until in an AD brain with cognitive symptoms almost all synaptosomes are affected.
To probe the mechanisms leading to differences between human and AD animal models in synaptic AD-related events, we analyzed synaptosomes isolated from cortical tissue of age matched strain-control and 5XFAD AD model mice. Using flow cytometry, in 5XFAD mice, despite robust human sequence Aβ plaque pathology, we observe only a small fraction of affected CN-PIB+ synaptosomes, which is not seen in the control mice. Future studies using flow isolation of interesting populations of synaptosomes from both humans and the 5XFAD mouse model will allow us to explore altered biochemical and genetic pathways to better understand the AD disease process and inform improvement of animal models.