Altered APP metabolism triggers changes in tau that cause dementia

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Research Abstract

Rare inherited forms of disease often reveal important information about more common sporadic forms of the same disease, and this is true for Alzheimer’s disease (AD). Typically, AD

is a disease of the elderly, however, a collection of autosomal dominant familial forms of AD (fAD) strike in late-mid life, but are otherwise very similar to sporadic AD. All cases of fAD are attributable to mutations in one of three genes: APP, PSEN1 or PSEN2. APP encodes for the amyloid precursor protein (APP) and the PSEN genes encode the active site of an enzyme for which APP is a substrate. APP is located on chromosome 21 and all persons with Down's syndrome (DS) develop AD neuropathology by their 30-40s, and if they live long enough virtually all DS adults become demented. Triplication of all or part of chromosome 21 is the main cause of DS and also leads to an increased life-long production of APP. This persuasive genetic evidence indicates that APP plays a central role in at least some forms of AD. Several proteolytic fragments of APP are suggested to be pathogenic and although it is uncertain which of these initiate the AD cascade, there is widespread acceptance that the microtubule-associated protein tau is critical for the proliferation of the disease process. Burgeoning data suggest that tau can spread from neuron to neuron in a highly stereotypic manner that is tightly linked to the emergence of symptoms in AD. However, little is known about the molecular identity of extracellular tau or the processes by which it is released from cells. We recently discovered that a variety of tau species are released from both primary rodent cortical neurons and human iPSC-derived cortical neurons (iCNs). We hypothesize that tau species released from wild type neurons have a physiological function, whereas we anticipate that additional, pathogenic tau species will be released from DS and fAD neurons. Since fAD carriers and persons with DS are predetermined to develop AD, we will use patient-derived DS and fAD iCNs as tools to identify pathogenic forms of tau. This will involve comparison of media and lysates of iCNs from non-demented controls, iCNs from DS and fAD gene edited cell lines with diploid expression of wild type APP, and mutant iCNs. These analyses will employ a battery of novel immunoassays to investigate the molecular identity of tau species. Using a unique library of DS, MCI, AD, and non-demented control CSF samples, we will validate the disease-relevance of changes detected in our iCNs. Thereafter, we will test if predicted pathogenic forms of tau induce the apoptotic phenotype seen in older cultures of DS and wild type iCNs when applied extracellularly. Given our expertise in iPSC technology, sophisticated tau detection systems, and access to unique patient samples, we expect to identify new biomarkers and provide important information for therapeutic targeting of pathogenic forms of tau.

Further information available at:

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