Molecular profiling of familial and sporadic Alzheimers disease

https://neurodegenerationresearch.eu/survey/molecular-profiling-of-familial-and-sporadic-alzheimers-disease/

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Molecular profiling of familial and sporadic Alzheimers disease

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Research Abstract

Project Summary Alzheimer’s disease (AD) is now feared more than cancer among the elderly, yet we still do not understand the mechanisms of neuronal cell death in AD well enough to know which pathways to target for therapy. Notably, rare cases of familial AD (FAD) cause a more aggressive clinical course than more common cases of sporadic AD (SAD), suggesting that

studying FAD cases may inform SAD pathophysiology. However, no one has ever studied this possibility on a molecular level with single neuron resolution. To this end, we used laser capture microdissection to harvest individual pre-tangle bearing frontal cortex layer III neurons from presenilin-1 (PS1)- linked FAD cases and SAD cases, as well as naïve, unlabeled neurons from aged control cases. We then used custom microarrays to compare gene expression profiles within each neuron. The most remarkable observation from this study was that FAD and SAD neurons displayed ~40-70% increases in the expression of several chaperones (e.g., DNAJA3/HSP40) and proteases (e.g., CLPP) that function in the mitochondrial unfolded protein response (mtUPR), a critical pathway for maintaining mitochondrial proteostasis that helps the cell counter mitochondrial stress. Moreover, we found evidence for mtUPR gene activation in pre-tangle bearing layer III neurons harvested from cases of amnestic mild cognitive impairment (aMCI), a putative prodromal stage of AD. These novel pilot data suggested that mitochondrial proteostatic stress is an early event in FAD and SAD and that the mtUPR is activated as a neuroprotective mechanism. However, when we induced mitochondrial proteostatic stress in human hNT neurons, these cells first displayed an up-regulation of mtUPR genes and then, paradoxically, underwent cell death. This response was highly reminiscent of the endoplasmic reticulum UPR, where sustained activation shifts a normally protective pathway to an apoptotic one. Additional in vitro studies showed that mtUPR+ neurons exhibited signs of mitochondrial fission, lysosomal accrual, and mitophagy prior to cell death. Given that one of the prominent theories in the field is that lysosomal/autophagy abnormalities contribute to neurodegeneration in both FAD and SAD, these findings suggest that mtUPR dysfunction in vulnerable neurons acts upstream of lysosomal perturbations to trigger a feed-forward cell death cascade. To test this novel hypothesis, we propose to expand upon our molecular profiling studies to show that neuronal mtUPR activation precedes lysosomal/autophagy activation during the progression of AD. We will then use mitochondrial proteostatic stressors +/- pharmacological interventions in human neuronal cultures to dissect the mechanistic role of mtUPR activation in mitochondrial fission, lysosomal dysfunction and cell death. Altogether, this proposal will establish chronic mtUPR activation as a pivotal early event in familial and sporadic AD and build the knowledge scaffold necessary to model and target this pathway as a disease modifying therapeutic.

Further information available at:

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