Alzheimer's Disease, PKMζ and the Mechanisms of Memory Maintenance

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Multiple pathologic mechanisms, including amyloid-β (Aβ) plaques, neurofibrillary tangles (NFTs), and neuroinflammation contribute to Alzheimer's disease (AD). How these affect the progressive loss of long-term memory (LTM), which is the cardinal symptom of AD, remains unclear. We have previously found that persistent increases in PKMζ protein maintain LTP and LTM in wild-type hippocampal neurons, and we have recently discovered that persistent PKMζ-KIBRA interactions form the basis of long-term memory maintenance. Here we show that this core memory maintenance mechanism is disrupted during AD.

Using postmortem tissue from aged AD patients and matched controls, we find that the expression of PKMζ protein in AD hippocampal lysates is markedly reduced.

We then examined the effect of Aβ accumulation on the distribution of PKMζ and KIBRA in aged APP/PS1 mice. In line with previous reports that measured PKMζ by immunoblot (Ma et al 2013; DOI: 10.1038/nn.3486), we also find that such mice exhibit greatly reduced PKMζ expression in lysates from their hippocampal CA1a regions.

Quantitative immunohistochemistry revealed a dramatic downregulation of PKMζ in all layers of the hippocampus and neocortex of 24-month-old APP/PS1 mice, compared to wild-type littermates. Similarly, aged APP/PS1 mice displayed robustly reduced levels of KIBRA protein in all layers of hippocampus and neocortex, suggesting that Aβ pathology disrupts PKMζ-KIBRA interactions.

These results suggest that within the brain regions that organize and encode LTM, Aβ accumulation dysregulates the core mechanism underlying the persistence of memory.