Molecular regulation of tau protein, tau mRNA, and Alzheimer's Disease

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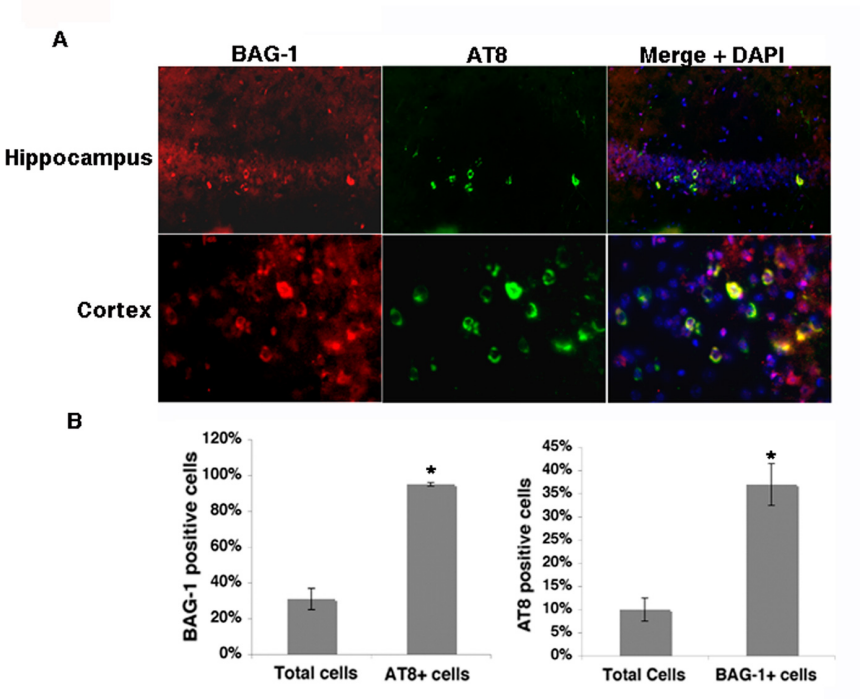
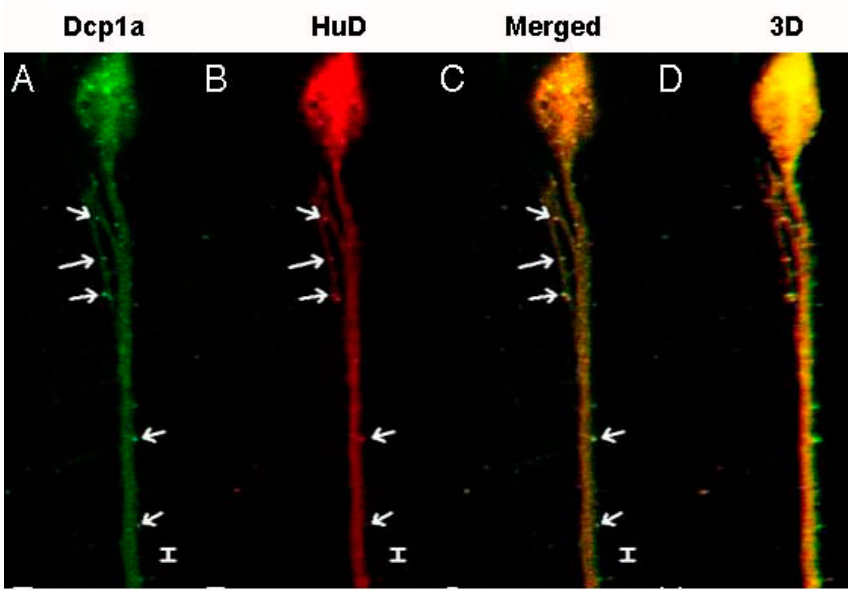
A major molecular pathology of Alzheimer's Disease (AD), and related dementias, is the intracellular accumulation of toxic tau protein. Tau protein is normally localized in the neuronal axon, where it associates with and stabilizes microtubules. Under pathological conditions, excess hyperphosphorylated tau protein is aggregated into insoluble filaments. This tau species is toxic and leads to cell death, and ultimately dementia of the patient. The expression, translation, and stabilization of tau protein are being studied to determine the mechanisms leading to the tau pathology. Cellular and animal models are employed to reconstruct the levels of regulation of tau protein translation and stabilization within the neurons. Postmordem tissue of Alzheimer's Disease patients are also studied to determine molecular mechanisms leading to the accumulation of tau protein. There are parallel projects being pursued at different levels of tau regulation to explore the pathology of tau protein and to find possible points of therapeutic intervention.

One project being pursued is the regulation of the degradation of tau protein. Tau protein degradation can be initiated by a group of intracellular proteins known as chaperones, including Hsp70. It has been suggested that upregulation of chaperone response in AD patients may induce degradation of the toxic tau protein, and therefore be therapeutic. In a screen for tau binding proteins, we identified BAG-1 as another protein which can bind in a complex with tau and Hsp70. However, induced overexpression of Bag-1 inhibits the normal degradation of tau protein, resulting in an increase in intracellular tau. Further studies have determined that BAG-1 is found located in tau tangles in both animal models of AD and in human patients with the disease. In addition, a specific isoform of BAG-1, is increased three-fold in patients with AD. Therefore, BAG-1 may play an important role in the pathology of AD and in the accumulation of tau protein.



BAG-1 and tau tangle colocalization in mouse model for Alzheimer's Disease
A.) Brain sections of Alzheimer's Disease model mice were analyzed by immunohistochemistry with primary antibodies AT-8 (a marker for tau tangles) and BAG-1. Nearly all AT8 positive neurons were also strongly reactive with the BAG-1 antibody B.) Quantitative analysis of AT8 positive and BAG-1 positive neurons from the 3XTg mouse model

Another project currently in progress, focuses on translation regulation mechanisms of tau mRNA in neurons. Previously we have demonstrated that tau protein and mRNA are found in axons. Tau mRNA is transported to axons in the form of a large RNP granule, which contains the HuD and IMP1 RNA binding proteins. HuD is a neuronally expressed isoform of the Hu protein family, and was shown to stabilize and protect tau mRNA from degradation. We found that both HuD and IMP1 colocalize with polyribosomes in sucrose gradient centrifugation analysis, and that these proteins affect the translation of tau mRNA. Recent experiments demonstrated that zinc, which is stored and released from glutamatergic neurons in the brain, inhibits translation and disrupts polyribosomes in P19 neurons. Simultanously, disruption of polyribosomes leads to impairment of the association between HuD, IMP1 with polyribosomes. In addition, we monitored the aggregation of Dcp1a, which serves as a P-bodies marker, in response to zinc application. P-bodies, also termed processing bodies, are found in various cells and functions as sites of mRNA storage and degradation. We monitored the presence of P-bodies in P19 neurons and in NGF treated PC12 cells, and their colocalization with HuD protein. These observations reveal a new mechanism of translation regulation by zinc, which is an endogenous neuronal substance, that may help understand pathologies such as epilepsy and brain injury where zinc release is believed to have a role.



P19 neurons were fixed and stained with antibodies against HuD RNA binding protein and Dcp1a protein (P-bodies marker).

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Acknowledgements

Prof. Irith Ginzburg holds the Sophie and Richard S. Richards Professional Chair in Cancer Research. Work is supported by the ISF (Israel Science Foundation) and by the Mario Negri Foundation.

We have internal support from the Benoziyo Center.