Cholinergic-associated loss of hnRNP-A/B in Alzheimer's disease impairs cortical splicing and cognitive function in mice.

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Abstract:

Genetic studies link inherited errors in RNA metabolism to familial neurodegenerative disease. Here, we report such errors and the underlying mechanism in sporadic Alzheimer's disease (AD). AD entorhinal cortices presented globally impaired exon exclusions and selective loss of the hnRNP A/B splicing factors. Supporting functional relevance, hnRNP A/B knockdown induced alternative splicing impairments and dendrite loss in primary neurons, and memory and electrocorticographic impairments in mice. Transgenic mice with disease-associated mutations in APP or Tau displayed no alterations in hnRNP A/B suggesting that its loss in AD is independent of Aβ and Tau toxicity. However, cholinergic excitation increased hnRNP A/B levels while in vivo neurotoxin-mediated destruction of cholinergic neurons caused cortical AD-like decrease in hnRNP A/B and recapitulated the alternative splicing pattern of AD patients. Our findings present cholinergic-mediated hnRNP A/B loss and impaired RNA metabolism as important mechanisms involved in AD.

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EMBO molecular medicine

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