Alteration of the microRNA network during the progression of Alzheimer's disease

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Research question and background

Alzheimer's disease (AD) is the most prevalent form of age-related dementias. The identification of mutations causing familial forms of the disease have greatly enhanced our understanding of the pathological mechanisms associated with these rare, inherited forms of AD. However, the fundamental biological processes underlying the development and progression of sporadic AD (>95% of AD cases is of sporadic origin) remain poorly understood. Increasing evidence links aberrant expression of microRNAs to neurodegenerative disorders including AD. The aim of our study is therefore to characterize the changes in the microRNA network during the development and progression of AD.

Methods and tissues used

We have generated expression profiles of ~700 microRNA species using the NanoString nCounter technology on the prefrontal cortex (PFC) of individuals with varying levels of AD neuropathology. More specifically, for each of the 7 Braak stages for neurofibrillary tangles, 7 samples were used, for a total of 49 samples. In this manner, we have been able to measure microRNA expression changes before, during and after the first neuropathological and clinical symptoms of the disease. We furthermore combined in situ hybridization and immunohistochemistry to analyze the expression of particular microRNAs in relation to AD neuropathology.

Results and conclusion

Profiling of microRNAs in the prefrontal cortex of a cohort of 49 patients grouped by Braak stages revealed 41 deregulated microRNAs. We focused on miR-132-3p, a microRNA that promotes synaptic plasticity. Down-regulation of miR-132-3p occurs already at Braak stages III and IV, before loss of neuron-specific microRNAs. Next-generation sequencing confirmed a strong decrease of miR-132-3p and of three related miRNAs encoded by the same miRNA cluster on chromosome 17. Deregulation of miR-132-3p in Alzheimer's disease brain appears to occur mainly in neurons displaying Tau hyperphosphorylation. By correlating microRNA changes with genome-wide gene expression data (Bossers et al, Brain 2010), we provide evidence that miR-132-3p may contribute to disease progression through aberrant regulation of mRNA targets in the Tau network.