Genetics: Genetics and omics of AD II

Alzheimer’s genetic risk factor FERMT2 (kindlin-2) controls axonal growth and synaptic plasticity in an APP-dependent manner

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Abstract

Background: Although APP metabolism is being intensively investigated, a large fraction of its modulators are yet to be characterized. In this context, we combined two genome-wide high-content screenings to assess the functional impact of miRNAs and genes on APP metabolism and the signaling pathways involved.

Method: We combined genome-wide high-content screenings to identify miRNAs (n = 2,555) and target genes (n = 18,107) involved in the APP metabolism. To predict the function(s) of miRNAs that target these genes, pathway enrichment analysis was performed using DIANA Tools mirPath (v3.0). CRISPR/Cas9 technology has been used to generate HEK293 cell lines carrying rs7143400 variant located in the FERMT2 3′UTR and its impact on miRNA binding. Involvement of FERMT2 in axonal growth and synaptic connectivity was assessed using primary neurons cultured in microfluidic devices that fluidically isolate axons from their cell bodies. The functional impact of FERMT2 on CA1 basal synaptic transmission and long-term potentiation (LTP) has been recorded in ex vivo mouse hippocampal slices, after stereotactic lentivirus injection allowing expression of shNT, shFERMT2 or shAPP.

Result: Our systematic approaches led us to characterize 180 genes targeted by 41 miRNAs as modulators of APP metabolism. Among these genes, we focused on FERMT2, a known genetic risk factor of sporadic AD. We found that FERMT2 directly interacts with APP to modulate its metabolism and that FERMT2 under-expression impacts axonal growth, synaptic connectivity and long-term potentiation in an APP-dependent manner. Lastly, the rs7143400-T allele, which is associated with an increased AD risk and localized within the 3′UTR of FERMT2, induced a down-regulation of FERMT2 expression through binding of miR-4504. This miRNA is mainly expressed in neurons and significantly overexpressed in AD brains compared to controls.

Conclusion: Altogether, our data provide strong evidence for a detrimental effect of FERMT2 under-expression in neurons and insight on how this may influence AD pathogenesis.