Protein-coding Circular RNAs identified in Alzheimer's Disease

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Background: Circular RNA is a unique class of closed-loop RNA that is more stable than its linear counterpart. As a result, circRNA transcripts could theoretically persist longer than mRNA, suggesting extended period of expression. Many recent transcriptomic analyses have revealed their regulatory roles in neural development and their dysregulation in neurodegenerative disorders. Their functional implications in disease progression remain poorly understood. Method: In this study, we investigated the expression pattern of circRNA transcripts in publicly available Alzheimer's datasets. The differentially expressed circRNAs were identified and analyzed to determine their encoded open reading frames. Bioinformatics analysis includes differential expression analysis of circRNA transcripts across publicly available Alzheimer's datasets, circRNA-derived open-reading frame prediction, and molecular dynamics simulations to assess their interactions with actin relative to the full-length SHROOM4. Results: We identified a circRNA transcript, hsa_circ_0090585, being upregulated in many Alzheimer's total RNA-seq datasets compared to healthy controls. This circRNA is predicted to encode truncated versions of the SHROOM4 protein, which we refer to as micropeptides. SHROOM4 is an actin-binding protein that has previously been suggested to regulate synaptic development. We hypothesize that the micropeptides encoded by the circular RNA transcript disrupt the normal function of the SHROOM4 protein. Preliminary molecular dynamics simulations indicate that these micropeptides interact with actin differently than the SHROOM4 protein, despite retaining the actin-binding domain. We have successfully expressed these micropeptides and are currently performing functional assays to determine experimentally to see if this interaction ultimately alters cytoskeletal dynamics in cells. Conclusion: Preliminary findings suggest that hsa_circ_0090585-derived micropeptides may competitively bind to actin against SHROOM4. Experimental work would further support a novel mechanism where circRNA encoded micropeptides contribute to the cytoskeletal dysregulation in Alzheimer's disease. This would highlight the translation of circRNA as another layer in the progression of neurodegenerative disorders. Functional assays will clarify the mechanism of this interaction.