Translated circular RNAs as potential contributors to Alzheimer's-type neurodegeneration

Giorgi Margvelani[1], Naghme Bagheri[1], Haining Zhu, Peter T Nelson[2], and Stefan Stamm[1]

[1] Department of Biochemistry, University of Kentucky, Lexington, KY, USA, [2] Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA, USA. [3] Department Pharmacology and Toxicology, University of Arizona, Tucson, AZ, USA

Circular RNAs (circRNAs) are covalently closed RNAs that are mostly generated through backsplicing by connecting a 5' splice site to an upstream 3' splice site. CircRNAs are highly expressed in brain. The expression levels of 14 circRNAs were associated with Alzheimer's disease stages.CircRNAs use N6-methyl adenosine and inosine RNA modifications for translational initiation. All investigated circMAPT RNAs (microtubule associated protein tau gene) express protein after adenosine to inosine modification. During Alzheimer's disease progression, we observed an increase of adenosine to inosine RNA editing in circular, but not linear RNAs, suggesting that some circRNAs are translated in vivo. FUS-mutants R495X and R521G that cause amyotrophic lateral sclerosis strongly promote circMAPT 12-7 translation, suggesting that mutated hnRNPs could act via circRNA translation. MAPT uses at least 75 backsplice sites, of which 69 are human-specific, generating 107 circMAPT isoforms. The circMAPT isoforms expressed most highly in human brain were generated by splicing between exon pairs: 4->1, 7->4, 9->4, 9->5, 12->7, and 12->10. These circRNAs encode proteins raging is size from 7 to 40 kDa. We demonstrated translation of the circMAPT 9->5, 12->7, and 12->10 isoforms. CircMAPT 12->7 and 12->10 encoded proteins promoted tau aggregation in vitro and circMAPT 9->5 encoded protein colocalized with neurofibrillary tangles in human brain. CircMAPT encoded proteins have an interactome distinct from mRNA encoded tau. Each of these observations implies a gain-of-toxic circMAPT function.In summary, most circMAPT-proteins are human-specific and Alzheimer's pathogenesis may promote their translation via RNA modifications. Some circMAPT-proteins promote aggregation of mRNA-encoded tau and could be an under-appreciated factor in Alzheimer's disease.

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Presenter Name and contact information:
Stefan Stamm
Department of Molecular and Cellular Biochemistry
University of Kentucky, College of Medicine
B159 Biomedical Biological Sciences Research Bldg.
741 South Limestone
Lexington, KY 40536-0509, USA
e-mail: stefan@stamms-lab.net