Translation Of Circular RNAs As Drivers For Alzheimer's Disease

Stefan Stamm

University of Kentucky, Lexington, KY ;
e-mail: stefan@stamms-lab.net

Background

Circular RNAs (circRNAs) are covalently closed, often human-specific RNAs. CircRNAs are metabolically stable, allowing them to accumulate RNA modifications. Increasing evidence shows that circRNAs can be translated, where most frequently RNA modifications such as m6A and inosine, promote ribosomal entry (reviewed in PMID: 39660652). We found that adenosine to inosine RNA modification result in the translation of circRNAs formed by the **MAPT** (microtubule associated protein tau) gene. mRNA-encoded MAPT proteins form neurofibrillary tangles (NFTs), the hallmark of Alzheimer's disease and related tauopathies. The circRNA-encoded proteins promote aggregation of mRNA-encoded tau protein in vitro (PMID: 36533443). RNA sequencing showed that during Alzheimer's disease (**AD**) progression in entorhinal cortex the deamination of adenosines to inosines (**A>I** modification) of circular RNAs strongly correlates with Braak stages, i.e. AD severity, which was not observed for mRNA (PMID: 37266374).

Results

Translation of circRNAs from the MAPT gene is strongly promoted by conversion of inosines to adenosines, catalyzed mainly by the cytosolic proteins ADAR1-p150. M6A modifications slightly enhance inosine-dependent translation. However, in contrast to other reported circRNAs, m6A modification is not sufficient for circMAPT-translation (PMID: 38286213). Almost all circRNAs from the MAPT gene are human specific (PMID: 38286213), reflecting that primate-specific Alu elements promote circRNA formation and interfere with translation. Importantly, AAV-mediated circMAPT expression in mouse brain using constructs with heterologous introns flanking the circRNA results in protein expression and AD-like pathology in hippocampus.

Our mouse studies indicate that translation of human-specific circRNAs occurs in vivo and could lead to an AD-phenotype. Our data support *the **hypothesis*** that human-specific circRNAs from the MAPT-gene are translated in neurons after RNA modification, possibly caused by the inflammation leading to RNA editing through ADAR1-p150. The circRNA-protein products cause aggregation of mRNA-encoded tau protein leading to neuronal death. Thus, targeting circMAPT RNAs using siRNAs (PMID: 39974901) and/or blocking their translation could be a new therapeutic avenue for AD.

Funding: 1R01AG095675-01, 1R21AG087332-01, MCB-2221921, NSF-BSF, all to SS.

Decoding the Roles of Oncogenic Coding circRNA in Metabolic Rewiring

Kuei-Yang Hsiao

Institute of Biochemistry, National Chung Hsing University

Circular RNAs (circRNAs) are single-stranded RNA molecules generated by backsplicing, representing a novel group of regulatory molecules. We previously identified an oncogenic circRNA derived from exons 2-3 of the SDHAF2 gene (circSDHAF2), which encodes a novel isoform with a modified helix 5 (SDHAF2mh5) through a splicing-dependent, exon junction complex-mediated translation mechanism. SDHAF2mh5 harbors novel sequences resulting from the backsplicing junction, including a predicted mitochondrial transit peptide and a disrupted 5th α-helix required for SDHA assembly, implying its contribution to SDH deficiency, an important characteristic in tumor cells. Both biochemical and cellular analyses demonstrated that SDHAF2mh5 localizes to mitochondria in colorectal and breast cancer cells. Consistent with its mitochondrial involvement, metabolomic profiling of circSDHAF2-expressing HCT116 cells revealed increased succinate and reduced complex II activity. Intriguingly, prompted by the elevated levels of succinate and malonyl-CoA -- natural inhibitors of lipid catabolism in mitochondria -- we discovered that circSDHAF2 facilitated prominent lipid-droplet accumulation. Mechanistically, inhibition of the mitochondrial α-ketoglutarate carrier SLC25A11, IDH1, or ACC suppressed lipid accumulation, indicating a carbon-flux rerouting from the tricarboxylic acid cycle toward fatty-acid synthesis via the SLC25A11-IDH1-ACC axis. This metabolic shift conferred a survival advantage during nutrient deprivation and chemotherapy stress. Under serum starvation, accumulated lipid droplets were consumed, suggesting their role as an alternative energy reservoir. Consistently, blocking lysosomal lipolysis impaired lipid-droplet catabolism and reduced cell viability. Notably, enhanced cellular fitness depended primarily on peroxisomal, rather than mitochondrial, β-oxidation. Taken together, these findings demonstrate that circSDHAF2 encodes a novel mitochondrial protein, reprograming TCA carbon flux toward fatty-acid synthesis and enhancing cellular fitness under stress. Targeting circRNA-derived hidden proteomes such as SDHAF2mh5 may open new therapeutic avenues in cancer treatment.

Keywords:

Coding circular RNA, SDHAF2, lipid metabolism, β-oxidation, TCA cycle

The Roles of circRNAs in Lung Adenocarcinoma.

By Mong-Lien Wang (Lotus Wang)

Lung cancer contributes to high cancer mortality worldwide with 80% of total cases diagnosed are non-small cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) tyrosine kinase (TK) domain serves as a druggable target in NSCLC patients with exon 19 deletion and L858R mutation. However, patients gain resistance to first- and second-generation EGFR-TK inhibitors through activation of T790M mutation. Third generation EGFR-TKI, Osimertinib exhibits high efficacy in patients with L858R/T790M mutations but they experienced acquired resistance thereafter. Circular RNAs (circRNAs) are non-coding products of backsplicing of pre-mRNAs which have been established to possess potent biological functions. Dysregulated circRNA expression has been linked to diseases including different types of cancer. The molecular pathways implicated in them are regarded as the targets of therapeutic interference. The involvements of specific circRNAs in oncogenic or tumor suppressive pathways have recently emerged. We previously identified hsa_circ_0000190 (C190) circRNA to be a negative prognostic biomarker of LC upregulated in EGFR mutant cells. Elevation of the C190 levels in patient plasma correlates with poor disease status and treatment response. We further investigated that through positively mediating oncogenic pathways, C190 enhanced tumor growth and cancer cell mobility, leading to fast tumor growth in vivo. On the other hand, we also identified another circular RNA that suppresses tumor progression and drug-resistance in lung cancer. Through understanding the diverse roles of circular RNAs in lung cancer, our study shed lights on a potential treatments strategy to control advanced lung adenocarcinoma tumors.