UKE Paper of the Month December 2023

MicroRNA-92a–CPEB3 axis protects neurons against inflammatory neurodegeneration

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ABSTRACT:

Neuroinflammation causes neuronal injury in multiple sclerosis (MS) and other neurological diseases. MicroRNAs (miRNAs) are important modulators of neuronal stress responses, but knowledge about their contribution to neuronal protection or damage during inflammation is limited. Here, we constructed a regulatory miRNA–mRNA network of inflamed motor neurons by leveraging cell type-specific miRNA and mRNA sequencing of mice undergoing experimental autoimmune encephalomyelitis (EAE). We found robust induction of miR-92a in inflamed spinal cord neurons and identified cytoplasmic polyadenylation element-binding protein 3 (Cpeb3) as a key target of miR-92a-mediated posttranscriptional silencing. We detected CPEB3 repression in inflamed neurons in murine EAE and human MS. Moreover, both miR-92a delivery and Cpeb3 deletion protected neuronal cultures against excitotoxicity. Supporting a detrimental effect of Cpeb3 in vivo, neuron-specific deletion in conditional Cbep3 knockout animals led to reduced inflammation-induced clinical disability in EAE. Together, we identified a neuroprotective miR-92a–CPEB3 axis in neuroinflammation that might serve as potential treatment target to limit inflammation-induced neuronal damage.

STATEMENT:.

In our study, we explored neuron-intrinsic resilience pathways to develop neuroprotective treatments for inflammatory neurodegeneration. Using cell-type specific miRNA and mRNA purification and sequencing in a mouse model of MS, we created a detailed neuronal miRNA-mRNA network for neuroinflammation. This unique approach revealed the neuroprotective miR-92a–CPEB3 axis and provides a resource for discovering other protective pathways and understanding cell-specific responses in multiple sclerosis and other neurodegenerative diseases associated with neuroinflammation.

BACKGROUND:

The work was mostly conducted by Dr. Iris Winkler who has been at the UKE since 2015. The main work was performed at the Institute of Neuroimmunology and Multiple Sclerosis (INIMS) under the supervision of Prof. Dr. Manuel Friese. The focus of the group is to understand the pathophysiology of MS and to develop new therapies. This work was a joint effort with groups from the UKE, the Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, and groups from Magdeburg, Göttingen, Taipei and Geneva. This project was funded by the DFG and the BMBF.