UKE Paper of the Month July 2024

STING orchestrates the neuronal inflammatory stress response in multiple sclerosis

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ABSTRACT:

Inflammation-induced neurodegeneration is a defining feature of multiple sclerosis (MS), yet the underlying mechanisms remain unclear. By dissecting the neuronal inflammatory stress response, we discovered that neurons in MS and its mouse model induce the stimulator of interferon genes (STING). However, activation of neuronal STING requires its detachment from the stromal interaction molecule 1 (STIM1), a process triggered by glutamate excitotoxicity. This detachment initiates non-canonical STING signaling, which leads to autophagic degradation of glutathione peroxidase 4 (GPX4), essential for neuronal redox homeostasis and thereby inducing ferroptosis. Both genetic and pharmacological interventions that target STING in neurons protect against inflammation-induced neurodegeneration. Our findings position STING as a central regulator of the detrimental neuronal inflammatory stress response, integrating inflammation with glutamate signaling to cause neuronal cell death, and present it as a tractable target for treating neurodegeneration in MS.

STATEMENT:

Our work opens a completely new view on how different external cues are integrated by neurons during CNS inflammation. Disentangling the neuronal inflammatory stress response holds the promise to develop new and specific neuroprotective intervention strategies for MS and other neurodegenerative diseases.

BACKGROUND:

This work was conducted at the Institute of Neuroimmunology and Multiple Sclerosis (INIMS) under the supervision of Prof. Manuel A. Friese. The INIMS' main interest is to study the interactions of the immune and nervous system. The project was part of the DFG-funded FOR2289 (FR1720/9-1 and FR1720/9-2 to M.A.F.). It was mostly performed by the Clinician Scientists Dr. Marcel S. Woo and Dr. Christina Mayer. The project was also supported by the "Deutsche Multiple Sklerose Gesellschaft" (DMSG; grant number V 6.2 to M.A.F.); Joachim-Herz-Foundation (850035 to M.S.W.) and Else Kröner Fresenius Memorial Stipend (2023_EKMS.03 to M.S.W.).