UKE Paper of the Month Juni 2019

Bassoon proteinopathy drives neurodegeneration in multiple sclerosis

Benjamin Schattling*, Jan Broder Engler*, Constantin Volkmann, Nicola Rothammer, Marcel S. Woo, Meike Petersen, Iris Winkler, Max Kaufmann, Sina C. Rosenkranz, Anna Fejtova, Ulrich Thomas, Aparajita Bose, Simone Bauer, Simone Träger, Katharine K. Miller, Wolfgang Brück, Kent E. Duncan, Gabriela Salina, Peter Soba, Eckart D. Gundelfinger, Doron Merkler and Manuel A. Friese

Nature Neuroscience

*equal contribution

ABSTRACT: Multiple sclerosis (MS) is characterized by inflammatory insults that drive neuroaxonal injury. However, knowledge about neuron-intrinsic responses to inflammation is limited. By leveraging neuron-specific messenger RNA profiling, we found that neuroinflammation leads to induction and toxic accumulation of the synaptic protein bassoon (Bsn) in the neuronal somata of mice and patients with MS. Neuronal overexpression of Bsn in flies resulted in reduction of lifespan, while genetic disruption of Bsn protected mice from inflammation-induced neuroaxonal injury. Notably, pharmacological proteasome activation boosted the clearance of accumulated Bsn and enhanced neuronal survival. Our study demonstrates that neuroinflammation initiates toxic protein accumulation in neuronal somata and advocates proteasome activation as a potential remedy.

STATEMENT: In this interdisciplinary effort, we set out to explore the neuronal response to inflammation in order to better understand neuronal injury and develop new neuroprotective strategies. By leveraging state-of-the-art technologies and multiple experimental systems we unveiled a fundamentally new concept for the pathomechanism of inflammation-induced neurodegeneration. We observed that inflammation is able to spark toxic neuronal protein aggregation, which in turn fosters neuroaxonal loss and shows striking similarities to Alzheimer's or Parkinson's disease. Thus, inflammation might trigger a neurodegenerative automatism that once activated propagate independently of the initial inflammatory insult. This provides a long sought-after explanation for the major clinical paradox in multiple sclerosis, why neurodegeneration progresses relentlessly despite anti-inflammatory treatments. Finally, we found a therapeutic strategy targeting protein aggregation to support neuronal survival, thus representing a new starting point for drug development in multiple sclerosis.

BACKGROUND: This work was primarily performed at the Institute of Neuroimmunology and Multiple Sclerosis headed by Prof. Dr. Manuel Friese in close collaboration with researchers from Hamburg, Magdeburg, Erlangen, Göttingen and Geneva. The work was spearheaded by the neurobiologist Dr. Benjamin Schattling and the bioinformatician Dr. Dr. Jan Broder Engler, who share the first authorship of the study. The work was funded by Deutsche Forschungsgemeinschaft, Oppenheim Förderpreis für Multiple Sklerose (Novartis), Else Kröner-Fresenius-Stiftung, Swiss National Science Foundation and the Helmut Horten Foundation and Gebert-Rüf Foundation.