T19-015C

CYTOSKELETAL CONTROL IN ADULT MICROGLIA IS ESSENTIAL TO RESTORE NEURODEVELOPMENTAL SYNAPTIC AND COGNITIVE DEFICITS

S. Kessels[1], C. Trippaers[1,2], B. Rombaut[1,3], A. Janssen[1], I. Hamad[1,4], K. Ramanathan[1], S. Duwé[1], M. Mertens[1], L. Berden[1,5], J. Beeken[1], S. Poovathingal[7,8], T. Voets[8,9], M. Kleinewietfeld[1,4], L. Nguyen[6], J.P. Antel[10], L.M. Healy[10], S.A. Cowley[11], K. Ishizuka[2], J.-M. Rigo[1], J. Hendrix[1], T. Vanmierlo[1,3], I. Dewachter[1], Y.A. Alpizar[1], A. Sawa[2], B. Brône[1]

[1] Hasselt University, BIOMED, Diepenbeek, Belgium; [2] Johns Hopkins University, Department of Psychiatry/Neuroscience/Pharmacology/Biomedical Engineering/Genetic Medicin/Mental Health, Baltimore, USA; [3] Maastricht University, Mental Health and Neuroscience Research Institute, Maastricht, Netherlands; [4] VIB Center for Inflammation Research, VIB Laboratory of Translational Immunomodulation, Diepenbeek, Belgium; [5] Belgian Nuclear Research Centre, Radiobiology Unit, Mol, Belgium; [6] ULiège, GIGA Institute, Liège, Belgium; [7] KU Leuven, Department of Neurosciences, Leuven, Belgium; [8] VIB Center for Brain & Disease Research, Leuven, Belgium; [9] KU Leuven, Laboratory of Ion Channel Research and TRP Research Platform Leuven, Leuven, Belgium; [10] McGill University, Department of Neurology and Neurosurgery, Québec, Canada; [11] University of Oxford, James and Lillian Martin Centre for Stem Cell Research, Oxford, UK

Neurodevelopmental disorders (NDDs), such as autism spectrum disorder and schizophrenia, are characterized by aberrant neural network assembly and synaptic dysfunction. While numerous NDD-associated genes, including NDEL1, LIS1, and Kal7, regulate cytoskeletal dynamics, their roles have predominantly been studied in neurons. However, microglia - the brain's resident phagocytes - also rely heavily on cytoskeletal organization to regulate intricate processes like synaptic elimination. Here, we investigate the role of Disrupted-in-Schizophrenia 1 (DISC1), an intracellular scaffold protein linking the cytoskeleton to neurodevelopmental signaling pathways, in microglial cytoskeletal dynamics and its impact on synaptic integrity and cognitive behavior. Raster image correlation spectroscopy in living microglia reveals a reduced diffusion speed of DISC1 in actin- and tubulin-rich cellular regions compared to cytoskeleton-free regions, indicating an interaction between DISC1 and the microglial cytoskeleton. Functionally, *Disc1*-deficient (*Disc1* locus impairment, *Disc1* LI) microglia exhibit decreased branch dynamics, reduced morphological complexity, and excessive uptake of synaptic proteins. These cytoskeletal disruptions in microglia correlate with synaptic abnormalities, including diminished excitatory transmission in the CA1 region of the hippocampus and spatial memory deficits in *Disc1* LI mice. Remarkably, reintroducing wild-type microglia via bone marrow transplantation in adult *Disc1* LI mice restores both synaptic function and cognitive performance, underscoring the reversible nature of these deficits. Our findings identify DISC1 as a pivotal molecular regulator of microglial cytoskeletal dynamics, linking its dysfunction to synaptic impairment and cognitive deficits characteristic of NDDs. This study highlights microglial cytoskeletal remodeling as a novel therapeutic target for ameliorating cognitive impairments, even in adulthood, offering new avenues for intervention in NDDs.