DEMENTIA
RESEARCH

SYNAPSIS FOUNDATION SWITZERLAND

Principal Investigator Grant

Project

Rosa Paolicelli
"Microglial TDP-43-dependent regulation of RNA splicing and cellular function in neurodegeneration"

Granted amount	CHF 300'000
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Main applicant

Rosa Chiara Paolicelli, PhD
Department of Biomedical Sciences (DSB)
University of Lausanne
Rue du Bugnon 7
1005 Lausanne

Microglial TDP-43-dependent regulation of RNA splicing and cellular function in neuro¬degeneration

Intracellular aggregates containing TDP-43 protein are commonly found in the brain of people affected by many different neurodegenerative disorders, ranging from Amyotrophic Lateral Sclerosis and Frontotemporal Dementia to Alzheimer's disease. However, despite the growing interest in this pathological feature, the molecular and cellular mechanisms underlying TDP-43 pathology are poorly understood. In particular, how TDP-43 dysfunction affects microglia, the innate immune cells of the brain, has been little investigated. Microglia play important roles in surveying neurons and maintaining brain homeostasis.

We have recently generated a mouse line in which TDP-43 is depleted specifically in microglia, and found that these mice display signs of neurodegeneration, suggesting that microglial TDP- 43 plays an important role in pathology. Here we propose to investigate the underlying mechanisms. We will first elucidate how loss of TDP-43 protein affects RNA processing, by analysing the microglial transcriptome both in murine and human microglia. Next, we will focus on the functional consequences, with a special attention on phagocytosis and lipid metabolism, which are both highly relevant for microglial function.

Finally, we will validate our findings in human samples from patients with TDP-43 pathology. Overall, this project will shed light on how microglial TDP-43 contribute to the pathogenesis of neurodegeneration.