University of Lausanne

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Title: Studying the role of microglial TDP-43 in myelin and motor dysfunction

Project description:

Microglia, the resident macrophages of the CNS, are implicated in a variety of biological processes and critically contribute to proper brain development and brain homeostasis across the life span. A growing body of evidence indicates that dysfunctional microglia might be implicated in the pathogenesis of brain disorders. TDP-43, encoded by the TARDBP gene, is a highly conserved DNA/RNA binding protein that shuttles between the nucleus and the cytoplasm. Its aberrant cytoplasmic aggregation, commonly associated with depletion of nuclear TDP-43, is a hallmark of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTLD). Importantly, TDP-43 inclusions have been reported not only in neurons, but also in glia, suggesting a key contribution of these cells to the etiology of TDP-43 proteinopathies. We have described that microglia lacking the RNA-DNA binding protein TDP-43 display enhanced phagocytic behavior and contribute to pathological synapse loss in the adult brain. However, the exact molecular mechanisms underlying microglia-induced brain dysfunction have not been fully elucidated.

Aim of the project: This project aims at investigating the molecular and cellular mechanisms of microglial TDP-43 dysfunction, addressing the downstream consequences of microglial TDP-43 depletion in the brain, and its long-lasting behavioral effects.

We have recently reported that the development of the motor and somatosensory cortex is impaired in mice lacking microglial TDP-43, with myelination deficits (unpublished data). By using a combination of histological and biochemical approaches, we will characterize the observed myelination abnormalities and will test the implication of candidate molecular players. We will complement in vitro approaches (primary cell cultures) with in vivo mouse models, to further studies the process of remyelination upon injuries, and test the role of microglial TDP-43 in such a context. Furthermore, we will investigate the long-lasting consequences on motor behavior. Overall, this study will contribute to the current understanding of the microglial roles in TDP-43 pathologies, and will help clarify the molecular and cellular mechanisms associated with microglia-induced myelin dysfunction.