FOR 1336

Pathogenic Role of Microglia and Macrophages in Frontotemporal Lobar Degeneration/Amyotrophic Lateral Sclerosis with TSP-43 Pathology

Funding Period:
from 2010 to 2016

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Project Description:

Frontotemporal lobar degeneration (FTLD) has been associated with abnormal activities of the transactive response DNA-binding protein 43 (TDP-43). Hyperphosphorylated fragments of TDP-43 are found in intracellular ubiquitinated inclusions, which are the hallmark of amyotrophic lateral sclerosis (ALS)-FTLD. Recently, TDP-43 was discovered to interact with the p65 subunit of nuclear factor (NF)-κB, which may induce neuroinflammation and neurodegeneration. In this project, we shall use transgenic mice with moderate and ubiquitous expression of human wild type TDP-43 or familial ALS-linked mutant TDP-43 (G348C) to study the pathogenic role of myeloid cells in FTLD. We shall interfere with TDP-43 function in microglia and macrophages by inactivating p65 or the NF-κB upstream regulator IκB kinase 2/β in myeloid cells, followed by an assessment of the impact on disease progression. In order to compare the results with the human pathology, we shall analyze post-mortem brain and spinal cord tissue from FTLD patients for neuroinflammatory changes. Moreover, we intend to generate induced pluripotent stem (iPS) cells from FTLD patients and characterize FTLD-iPS-derived microglial cell lines functionally.

Reference: https://gepris.dfg.de/gepris/projekt/165179216