Role of the transcriptional co-activator PGC-1α in the pathogenesis of clinical and experimental ALS

Call for projects 2009
Grant: 100 000 €
Project Duration: 2 years

Investigators: Patrick Weydt, University of Ulm, Germany

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Genetic modifiers, i.e. genes that modulate the onset and course of a disease, are among the most important clues for the identification of therapeutic targets in neurodegenerative diseases in general and ALS in particular. Dysfunction of PGC-1α a transcriptional coactivator can lead to impaired regulation of the mitochondria, the „power plants“ in neurons and all other cells of the body, and this is thought to be key to the energy deficit in neurodegeneration.

With our project we showed that genetic variants in the gene coding for PGC-1α are associated with a much earlier onset of the disease and a more rapid progression in ALS patient. In addition we modelled the PGC-1α modifier effect in transgenic mouse models to elucidate its mecanism of action. Analysis of spinal cord tissue from ALS mice with and without PGC-1α expression suggests that levels of the well known neuroprotective factor VEGF-A is one player in the signalling cascade. The therapeutic implications are now being evaluated.

ROLE OF THE TRANSCRIPTIONAL CO-ACTIVATOR PGC-1A IN THE PATHOGENESIS OF CLINICAL AND EXPERIMENTAL ALS

P. Weydt, K Braunstein, Germany
Grant: € 100 000

The present pilot grant will explore the mechanisms leading to the metabolic energy deficit in ALS. We build on our recent work on Huntington's disease, a related devastating adult onset neurodegenerative disease. We have identified PGC-1a as a key player in the regulation of energy balance of transgenic models of Huntington's disease and – importantly – also in Huntington's disease patients. Huntington's disease patients and ALS patients share several striking clinical and cellular features, such as muscle wasting and mitochondrial deficits, that suggest some shared pathogenic pathways. In addition transgenic mouse models of ALS and Huntington's disease also show metabolic similarities,e.g. muscle wasting and temperature dysregulation, that suggest that advances can be transferred from one disease to the other. Using transgenic animals we will study how the lack of metabolic regulator PGC-1a affects the course of ALS and whether interventions, such as drugs and exercise known to upregulate PGC-1a have a beneficial effect on ALS. In a concurrent genetic modifier study we will explore critical question, whether certain variants in the PGC-1a gene and which we have demonstrated to delay the progression of Huntington's disease have a similar effect in ALS patients.

TEAM

The present project is led by two junior investigators from the University of Ulm. Patrick Weydt is a clinician/scientist at the Department of Neurology, led by Pr Albert Ludolph.

He is currently completing his specialization as a neurologist. He is working both clinically and experimentally on neurodegenerative disease with a special focus on ALS and Huntington's disease. He is one of the co-discoverers of the role of the metabolic regulator PGC-1a on neurodegeneration in Huntington's disease. His ALS work focuses on the role of microglia and neuroinflammation in motorneuron degeneration. He has also studied the therapeutic potential of cannabinoids (the active ingredients of Marijuana) on ALS.

Kerstin Braunstein is a newly minted post-doc in the Departement of Experimental Neurology at the University of Ulm. She has extensive experience with mouse models of neurodegeneration. A special focus is on the behavioral characterization of mouse models of motorneuron disease.