

Press Release

New findings on the pathogenesis of amyotrophic lateral sclerosis and frontotemporal dementia

Scientists of the Hertie Institute for Clinical Brain Research (HIH), University Medical Center Tübingen (University Tübingen, Germany) have identified a new mechanism that could be involved in the formation of frontotemporal dementia development (FTD) and amyotrophic lateral sclerosis (ALS). They discovered that the absence of the nucleic acid binding protein TDP-43 within the cell causes a downregulation of the enzyme HDAC6. HDAC6 plays a regulatory role in important cellular processes, especially in the elimination of cytotoxic proteins. Without presence of this protein the rate of apoptosis is increased. In Germany approximately 10,000 patients are affected by these degenerative diseases of the neuronal system of which the causes remain unclear until now.

The disease relevant function of the FTD/ALS associated protein TDP-43 was first described in this study shown in the advance online publication of the EMBO journal (European Molecular Biology Organization).

The protein TDP-43 has a nuclear localization in healthy cells.

In 2006 scientists identified TDP-43 as a central component of pathological protein aggregate formations in affected neurons of FTD and ALS patients. Furthermore it was shown that TDP-43 was not localized in the cell nucleus of affected cells assuming that with the loss of TDP-43 in neurons an essential factor was missing as the study reports.

The scientists supervised by Prof. Dr. Philipp Kahle eliminated TDP-43 from the cells by silencing. In a genome wide microarray screening of all potential TDP-43 target genes in human cells it was observed that the absence of the nucleic acid binding protein TDP-43 results in a downregulation of the enzyme HDAC6. These findings could be confirmed by scientists of the RWTH Aachen (Germany) who performed studies with the TDP-43 knockout *Drosophila melanogaster* as an animal model. In collaboration with an industrial partner (Beckman Coulter Biomedical GmbH, Munich, Germany) an innovative technology was applied to quantify mRNA expression in the diminutive brains of just hatched fruit flies. HDAC6 is involved in the regulation of important cellular processes, especially on the elimination of toxic proteins. Indeed, the scientists were able to show that the functionality loss of TDP-43 and the related downregulation of HDAC6 results in an increased rate of apoptosis when the cell is exposed - this mechanism might thereby contribute to pathogenesis of FTD/ALS.