MedicalXpress

Important role of nucleocytoplasmic transport in amyotrophic lateral sclerosis and frontotemporal dementia

February 12 2016

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two devastating adult-onset neurodegenerative disorders. No cure exists for these diseases. Ten percent of ALS patients suffer from a familial form of the disease, while FTD is caused in 40% of patients by a genetic defect. In 2011, the most important genetic cause of ALS and FTD was discovered. The causative mutation was a repetition of a piece of non-coding DNA, a so called tandem repeat, in a gene with an unknown function, named C9orf72. A team of scientists from VIB and KU Leuven now discovered that proteins translated from this tandem repeat interfere with the nucleocytoplasmic transport which they found is essential for causing ALS and FTD.

Prof. Ludo Van Den Bosch (VIB/KU Leuven): "This is the first time that we see a role for nucleocytoplasmic transport for these specific forms of ALS and FTD. Moreover, these insights have a solid basis, since they come from 4 different scientific angles. It is an important next step in our understanding of these terrible diseases."

ALS and FTD

In ALS, motor neurons in the motor cortex, brainstem and spinal cord are affected, while in FTD cortical neurons in the frontotemporal cortex of the brain degenerate. Patients can have a clinical presentation that is predominantly motor (ALS), predominantly frontotemporal (FTD), or a

mixture of both (ALS-FTD). The motor problems consist of muscle weakness and paralysis, which is progressive and is usually fatal within 3 to 5 years after onset of the disease. FTD patients show behavioral and/or personality changes or language problems.

A tandem repeat in gene C9orf72

The causative tandem repeat in the gene C9orf72 is a GGGGCC hexanucleotide repeat expansion which could lead to a decrease in the C9orf72 protein level. Moreover, the repeat-containing RNA could be toxic, eventually by sequestering RNA-binding proteins in the nucleus. Last but not least, the so-called dipeptide repeat proteins (DPRs) translated from these repeat-containing RNA could also cause toxicity. These DPRs are translated by an unconventional non-ATG mediated form of translation from the hexanucleotide repeats in all three reading frames. As this process can also occur from the antisense transcript, a total of five different DPRs are found in C9orf72 patients.

PhD student Steven Boeynaems and Dr. Elke Bogaert under direction of prof. Ludo Van Den Bosch and prof. Wim Robberecht (VIB/KU Leuven) investigated whether and how these different DPRs could be toxic. Therefore, the researchers designed expression constructs that only express one DPR. Using yeast and fruit fly models, they discovered that only two of these DPRs were toxic, namely the glycine-arginine and proline-arginine DPRs. The scientists next investigated how these DPRs were toxic using genetic tools available in yeast and fruit fly. In collaboration with Dr. A. Gitler (Stanford University, USA), genome-wide genetic modifier screens were first performed in yeast. These screens were strongly enriched for genes controlling nucleocytoplasmic transport. Using fruit fly, the researchers confirmed the importance of this process. The most potent modifier was the import factor, transportin-1. This protein normally transports many RNA-binding proteins from the cytoplasm to the nucleus. This process was altered in

the transgenic fruit flies as these showed cytoplasmic accumulation of RNA-binding proteins. Moreover, they found that in brains of C9orf72 patients transportin-1 cargoes were also mislocalized. Bioinformatic analyses suggest that glycine-arginine and proline-arginine repeats could mimic the nuclear localization signals of these proteins and hence hijack nuclear import by overloading the nucleocytoplasmic transport system.

Prof. Wim Robberecht (VIB/KU Leuven): "Recently, two other papers were published in *Nature* using fruit flies containing C9orf72 repeats, yielding both toxic repeat RNA and toxic DPRs and these also concluded that defective nucleocytoplasmic transport is important in C9orf72 ALS and/or FTD. Interestingly, most patients with ALS and/or FTD, including the ones with C9orf72 hexanucleotide repeats, have aberrant cytoplasmic aggregates of normally nuclear RNA-binding proteins. As a consequence, modulating nucleocytoplasmic transport could become a promising and new therapeutic avenue."

More information: Steven Boeynaems et al. Drosophila screen connects nuclear transport genes to DPR pathology in c9ALS/FTD, *Scientific Reports* (2016). DOI: 10.1038/srep20877

Provided by VIB (the Flanders Institute for Biotechnology)