Genetic dissection of TDP-43 signaling in a *Drosophila* model of ALS

Frank Hirth, London, UK

Grant: 120 000 €

Recently it was shown that abnormal aggregates found in affected nerve cells of ALS patients are enriched with TDP-43 protein (Tar DNA binding protein of 43 kDa), and that several familial as well as sporadic ALS patients have a mutation in the coding gene. These findings strongly suggest that dysfunction of TDP-43 is causally related to ALS formation. However, the underlying mechanisms are not understood.

The fruitfly *Drosophila* is an ideal model system to study ALS. Although the fly has a less complex central nervous system than humans, the major building blocks are comparable, especially motor neurons and muscle innervation. *Drosophila* encodes a TDP-43 protein that is similar to the human protein affected in ALS.

We have mutated *Drosophila* TDP-43 and found that flies develop ALS-like symptoms, including impaired locomotion, progressive nerve cell loss and premature death.
To understand how and why these defects occur, we have searched for interaction partners of TDP-43 and identified targets that play a role in motor neuron function and muscle innervation.
In our research project, we propose to study the interaction between TDP-43 and these partners in detail and characterise their role during TDP-43 dysfunction.
We will then translate our findings to the human condition and investigate whether similar changes occur in ALS patients. Our experiments will verify targets of TDP-43 function and enable us to understand how ALS develops when the function of TDP-43 is affected. This in turn will identify therapeutic targets that can directly guide clinical research and the development of novel strategies for the targeted treatment of TDP-43-related ALS.

DrosALS - Genetic dissection of TDP-43 signaling in a *Drosophila* model of ALS

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Cytoplasmic accumulation and nuclear clearance of TDP-43 characterize familial and sporadic forms of amyotrophic lateral sclerosis and frontotemporal lobar degeneration, suggesting that either loss or gain of TDP-43 function, or both, cause disease formation. Here we have systematically compared loss- and gain of function of *Drosophila* TDP-43, TAR DNA Binding Protein Homolog (TBPH), in synaptic function and morphology, motor control, and age-related neuronal survival. Both loss and gain of TBPH severely affect development and result in premature lethality. TBPH dysfunction caused impaired synaptic transmission at the larval neuromuscular junction and in the adult. Prolonged loss and gain of TBPH in adults resulted in synaptic defects and age-related, progressive degeneration of neurons involved in motor control. Toxic gain of TBPH did not downregulate or mislocalize its own expression, indicating that a dominant-negative effect leads to neurodegeneration similar to mutational inactivation of TBPH. Together these data suggest that dysfunction of *Drosophila* TDP-43 initiates a loss-of-function phenotype whereby impaired synaptic transmission results in defective motor behavior and progressive deconstruction of neuronal connections, ultimately causing age-related neurodegeneration.

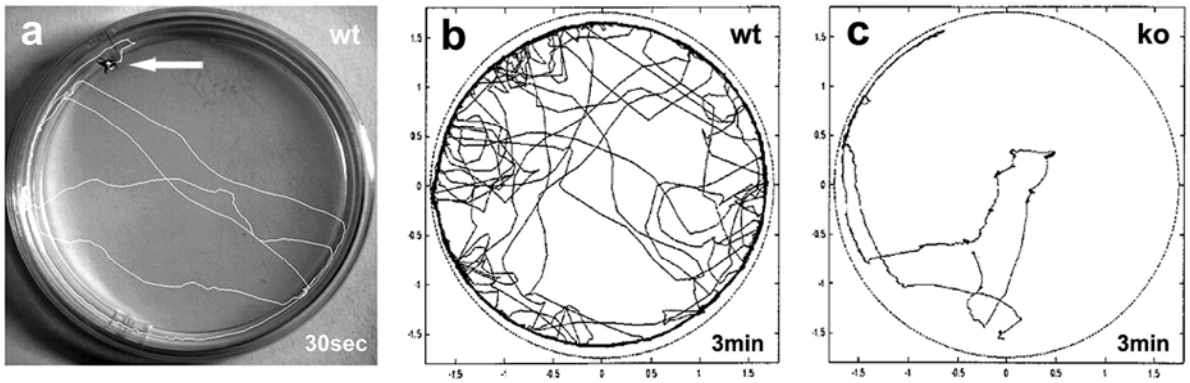

Figure 1. A fruitfly model of TDP-43 dysfunction reveals defective motor behavior due to TDP-43 dysfunction. (a) A normal wildtype fly in an arena (here a petri dish) and its movement trajectory (white line) can be visualized with a camera and a computer program. **(b)** Movement trajectory of a normal wildtype fly recorded over 30min. **(c)** A fly mutant for the ALS-related TDP-43 gene ("ko = knockout") shows severely reduced motor activity (compare to a normal fly in b). Quantitative analysis of motor behavior allows the study and genetic analysis of the pathogenic mechanisms underlying TDP-43 dysfunction in ALS.