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Keywords
Neurodegeneration – amyotrophic lateral sclerosis – pathophysiology - mouse model – drosophila model

Science

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the predominant loss of motor neurons in the motor cortex, brain stem and spinal cord. This results in progressive muscle weakness, atrophy and ultimately death of the patient due to respiratory failure. ALS patients have a life expectancy of only 2-5 years after diagnosis. The life-time risk for ALS is 1 in 300 and it typically affects adults in mid-life. In the vast majority (90 %) there is no familial history (sporadic ALS: SALS), while in a subset of patients (10 %) an underlying genetic cause is present (familial ALS: FALS). Clinically, both forms of ALS are indistinguishable. FALS has almost always an autosomal dominant inheritance pattern with mutations in the superoxide dismutase 1 (SOD1) gene as the most frequent cause accounting for 20 % of FALS. Both *in vitro* and *in vivo* model systems have been created in which the deleterious effect of mutant SOD1 was studied. However, the exact pathogenic mechanism underlying mutant SOD1-induced motor neuron death is not yet elucidated which has led to the consensus that the cause of ALS is multifactorial and a number of possible mechanisms have been proposed. These include oxidative stress, axonal transport defects, toxicity from intracellular protein aggregates, mitochondrial dysfunction, inflammation, decreased availability of growth factors and excitotoxicity. Recently, mutations in two new disease-causing genes have been identified: "TAR DNA binding protein" (TARDBP or TDP-43) and "fused in sarcoma/translocated in liposarcoma" (FUS/TLS). TDP-43 and FUS have striking structural and functional similarities. Both are multifunctional proteins that have been implicated in several steps of gene expression regulation, including transcription, RNA splicing, RNA transport and translation. This adds another possible contributing pathogenic mechanism to the list: disturbances in the RNA or DNA metabolism. However, how mutations in both FUS and TDP-43 cause motor neuron disease is still unknown. In this project, we will focus on the role of mutant FUS (mt FUS) in ALS. FUS is ubiquitously expressed and is predominantly localized in the nucleus, although cytoplasmic localization has been described for most cell types. FUS mutations have been recently discovered and account for approximately 3-4 % of FALS cases. In the Belgian FALS population, we have identified a family with a R521H mutation. Most of the known FUS mutations are dominantly inherited and localized in the C-terminal part of the protein. Neuropathological examination of the brain and spinal cord of ALS patients with mutations in FUS has revealed cytoplasmic

aggregates in neurons. Today, it is unclear whether FUS mutations lead to motor neuron loss through a gain of a toxic property or a loss of endogenous function, or a combination of both mechanisms. The loss of endogenous function can arise from the FUS protein inclusions and the concomitant disruption of its interactions with protein partners or RNA targets. Upon today, no animal models are available to study the mt FUS induced motor neuron degeneration. Our aims:

1. We will create animal models for mt FUS related ALS.

2. We want to clarify the pathogenic mechanism through which FUS mutations lead to selective motor neuron loss. More specifically, we will investigate the nature of the mutations: loss or gain of function mutations. In addition, we will elucidate which cell types, neurons and/or non-neuronal cells or a combination of both, are involved in this pathogenic mechanism. Finally, we aim to identify the molecular mechanism(s) involved in the pathogenic mechanism.

Selected publications

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