ALS as a Model System for Studying Degenerative Brain Diseases

https://neurodegenerationresearch.eu/survey/als-as-a-model-system-for-studying-degenerative-brain-diseases/

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Sweden

Title of project or programme

ALS as a Model System for Studying Degenerative Brain Diseases

Source of funding information

The Wallenberg Foundations

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Start date of award

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Total duration of award in years

5.0

The project/programme is most relevant to:

Motor neurone diseases

Keywords
Research Abstract

The common denominator for all fatal neurodegenerative diseases is the formation of protein aggregations in affected neurons. The role of these aggregations remains elusive due to the intrinsic difficulty of studying the molecular behavior of proteins inside living cells. We here present a plan for overcoming this problem. Our model system is amyotrophic lateral sclerosis (ALS), associated with misfolding and aggregation of the ubiquitous enzyme superoxide

dismutase-1 (SOD1). Using a novel epitope-mapping approach, we recently observed in transgenic ALS model mice that SOD1 aggregates are of two types with distinct molecular structures: type A and type B. The key feature of type A and type B aggregates is that they are associated with different severities of disease progression. These in vivo aggregates are different to those produced in earlier in vitro models. Analysis of different to those produced in earlier in vitro models. Analysis of aggregate patterns in different parts of the CNS suggests a local initiating event which subsequently spreads. The structural polymorphism shows that living cells not only control how SOD1 aggregates, but that the outcome of this control can vary with direct effect on ALS pathogenesis and prognosis. This new link between aggregate structure and in vivo pathology presents a unique handle on the role of protein deposition in disease. Of importance is to identify which aggregate properties modulate the toxic response. Is it their ability to destabilize cellular components, their propensity to spread new seeds, and/or simply their resistance to cellular turn-over? To find out, we will use a combination of aggregate structure mapping in vivo, CNS seeding and mouse strain crossing experiments, and atomic-resolution analysis of SOD1 misfolding and aggregation inside living neurons by NMR. Our multidisciplinary approach targets the missing gap between neural damage and high-resolution protein structure, which is the key obstacle for the development of effective treatments for degenerative diseases.

Lay Summary
Further information available at:

Types:
Investments > €500k

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Sweden

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Motor neurone diseases

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2016

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