Cellular aspects of protein misfolding in neurodegenerative diseases

https://neurodegenerationresearch.eu/survey/cellular-aspects-of-protein-misfolding-in-neurodegenerative-diseases/

Title of project or programme

Cellular aspects of protein misfolding in neurodegenerative diseases

Principal Investigators of project/programme grant

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- United Kingdom

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Medical Research Council

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The project/programme is most relevant to

- Huntington’s disease

Keywords

Research abstract in English

Aggregation of misfolded proteins is a characteristic of several neurodegenerative diseases. The huntingtin amino-terminal fragment with expanded polyglutamine repeat (polyQ) aggregates both in the cytoplasm and the nucleus. We recently discovered that aggregation of a protein containing a

polyQ stretch of pathological length is abolished when its expression is targeted to the endoplasmic reticulum or mitochondria. Preventing aggregation of a paradigmatic aggregation prone protein while achieving high levels of expression is a striking finding. Our data imply that polyQ aggregation is a property restricted to the nucleo-cytosolic compartment and suggest the existence of compartment-specific co-factors promoting or preventing aggregation of pathological proteins. We have not ruled out the existence of anti-aggregation factors preventing polyQ aggregation in the ER and the mitochondria, but we have recently identified a nucleo-cytosolic aggregation enhancer. While it is clear from in vitro studies that aggregation propensity of pure polyQ peptides is extremely high, in inclusions of Huntington s disease patients, Huntingtin amino-terminal fragments contain additional sequences. The polyQ expansion in Huntingtin is immediately followed by a proline-rich region and we found that this region strongly antagonizes aggregation. Thus, in the context of the amino-terminal fragment of Huntingtin, some trigger ought to be required to alleviate this inhibition and convert the soluble protein into an aggregation-prone one. We found that while a protein needs to be unfolded to be degraded, uncoupling unfolding and degradation promotes accumulation of aggregation-prone folding intermediates. We propose that uncoupling unfolding and degradation triggers misfolding of mutant Huntingtin. This uncoupling event might also be involved in other neurodegenerative diseases, an hypothesis we are currently testing. Indeed, several lines of evidence indicate that different neurodegenerative diseases might arise from a common molecular mechanism. Seeking further experimental support for this model, we have undertaken to analyze the effect of specific chemical compounds curing yeast Prions in cellular models of Huntington’s disease and found 2 active compounds, one of them being a marketed drug. These compounds might define a new class of anti-amyloidogenic-proteins compounds because they do not act directly on the aggregates but might rather enhance clearance of the soluble pathogenic fragment of Huntingtin. We are continuing to explore the cellular pathway responsible for this effect. Identification of a cellular pathway enhancing the cell s ability to remove abnormal proteins might have some therapeutic benefit.

Lay Summary