Cellular aspects of protein misfolding in neurodegenerative diseases

https://neurodegenerationresearch.eu/survey/cellular-aspects-of-protein-misfolding-in-neurodegenerative-diseases-2/

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Country

United Kingdom

Title of project or programme

Cellular aspects of protein misfolding in neurodegenerative diseases

Source of funding information

MRC

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14/08/2011

Total duration of award in years

5.0

The project/programme is most relevant to:

Neurodegenerative disease in general

Keywords
Research Abstract
The deposition of misfolded proteins is the hallmark of the late onset, rapidly progressive and devastating neurodegenerative diseases including Alzheimer's, Parkinson's, Huntington's and amyotrophic lateral sclerosis. These diseases are caused by a gain of toxic properties associated with the propensity of otherwise soluble proteins to misfold. Neurodegenerative diseases usually strike in mid-adult life, while the disease-causing proteins are expressed

throughout the entire life implying that these misfolded-prone proteins are actually benign for decades. What governs the switch from the soluble and harmless conformation to a misfolded and deleterious one is unclear. We are aiming at understanding what triggers this pathological conformational switch as it is one of the earliest events in the etiology of neurodegenerative diseases. We have recently discovered that mutant SOD1 aggregates, associated with amyotrophic lateral sclerosis, penetrate inside cells and replicate their misfolded state indefinitely, just like prions. Using a combination of approaches and mole systems, we are aiming at identifying the mechanisms underlying the prion-like propagation of misfolded proteins. In addition, we aim at identifying novel strategies that could lead to correct conditions caused by misfolded proteins. Recently, have discovered a novel and selective way to rescue cells from stress caused by misfolded proteins. We have identified a small molecule, guanabenz, which binds to a regulatory subunit of protein phosphatase 1, PPP1R15A/GADD34, selectively disrupting the stress-induced dephosphorylation of the alpha subunit of translation initiation factor 2 (eIF2?). Without affecting the related PPP1R15B-phosphatase complex and constitutive protein synthesis, guanabenz prolongs eIF2? phosphorylation in stressed cells, thereby adjusting the protein production rates to levels manageable by available chaperones. This favours protein folding and thereby rescues cells from protein misfolding stress. This suggests that inhibition of PPP1R15A could ameliorate protein misfolding diseases. We will est this attractive possibility. In addition, having provided the proof of principle that serine/threonine phosphatases are drug targets, we aim to investigate the detailed molecular mechanism by which guanabenz selectively inhibits PPP1R15A/GADD34, using a combination of approaches Ultimately, the knowledge emanating from our work will serve to ameliorate human health and disease.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Neurodegenerative disease in general

Years:
2016

Database Categories:
N/A

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