Molecular Chaperones and Small Molecules

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Country

USA

Title of project or programme

Molecular Chaperones and Small Molecules

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,131,963.30

Start date of award

01/02/2008

Total duration of award in years

2

The project/programme is most relevant to:

Huntington's disease

Keywords

Heat-Shock Proteins 70, Molecular Chaperones, polyglutamine, BAG3 gene, small molecule

Research Abstract

DESCRIPTION (provided by applicant): Heat shock protein 70 (Hsp70) is a molecular chaperone that plays a central role in protein quality control (PQC). Hsp70 is considered a “”triage chaperone”” because it is important in protein folding, while it also blocks aggregation and targets misfolded proteins for degradation by the ubiquitin proteasome system (UPS) and the chaperone-mediated autophagy (CMA) pathway. How does Hsp70 “”decide”” if a protein can

be folded? What molecular and structural mechanisms link Hsp70 to the various fates of its protein substrates? These questions are essential to our understanding of how cells maintain protein homeostasis (i.e. proteostasis). Based on the findings obtained in the first funding cycle (2008-present), we have developed a model in which the dwell time of a substrate in the Hsp70 complex might be one factor that contributes to whether a protein is ultimately folded or degraded. This model emerged from experiments in which we used high throughput screening (HTS) to uncover new chemical probes that “”tune”” the ATPase activity of Hsp70. Using these molecules, we showed that inhibiting ATP turnover favored degradation of multiple Hsp70 substrates, such as tau and polyglutamine (polyQ) expanded huntingtin (polyQ-Htt) and androgen receptor (polyQ-AR), while stimulating activity led to substrate accumulation and proteotoxicity. Because ATP turnover in Hsp70 is allosterically linked to substrate affinity, we now hypothesize that prolonged interactions with Hsp70 may be a molecular “”trigger”” that favors recruitment of UPS components. In the proposed work, we will explore this idea in the following specific aims: (1) develop a suite of chemical probes and point mutants that trap Hsp70 in either its tight or loose affinity forms, (2) explore the role of substrate affinity in stabilization of te unfolded model proteins, tau and polyQ-Htt, and (3) understand how Hsp70 discriminates between normal AR and misfolded, polyQ-AR. From these studies, we expect to better understand how Hsp70 makes key triage decisions. This study is significant because Hsp70 has been linked to many protein-misfolding diseases, including neurodegenerative disorders. Thus, the proposed studies will clarify the logic of Hsp70-mediated PQC and, perhaps, suggest new methods for treating these diseases. This work is innovative because we will use a comprehensive chemical biology approach, combining new chemical probes with point mutants and cell-based models of disease to explore fundamental mechanisms of PQC.

Lay Summary
PUBLIC HEALTH RELEVANCE: Neurodegenerative disorders, including Huntington’s disease (HD), are devastating, progressive diseases that have no known cure. These diseases are thought to involve an imbalance in protein quality control (PQC) that allows accumulation of misfolded protein. The proposed work explores whether the heat shock protein 70 (Hsp70) could be an under-explored therapeutic target for HD and other protein misfolding diseases.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A