ROLE OF CHAIN LENGTH AND SEQUENCE CONTEXTS ON POLYGLUTAMINE OLIGOMERIZATION

https://neurodegenerationresearch.eu/survey/role-of-chain-length-and-sequence-contexts-on-polyglutamine-oligomerization/

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Country

USA

Title of project or programme

ROLE OF CHAIN LENGTH AND SEQUENCE CONTEXTS ON POLYGLUTAMINE OLIGOMERIZATION

Source of funding information

NIH (NINDS)

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01/07/2006

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5

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington gene, polyglutamine, S Phase, Length, Huntington Disease

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a devastating neurodegenerative disease that is caused by mutational expansion of the CAG codon in exon 1 of the huntingtin (Htt) gene. The CAG repeat expansion leads to an expanded polyglutamine domain in the N-terminal region of the huntingtin protein. N-terminal fragments of Htt (Htt-NTFs) are generated by proteolysis of the full-length protein or by aberrant splicing of mutant mRNA transcripts. These fragments end up as insoluble intranuclear inclusions within medium spiny and cerebellar neurons. Htt-NTFs encompass a 17-residue N-terminal stretch (N17), a polyQ domain, and a 38-residue proline-rich C-terminal stretch (C38). We have shown that the N17 stretch accelerates fibril formation whereas the C38 stretch destabilizes insoluble fibrils and stabilizes large soluble spherical aggregates. Recent studies in transgenic mice show that the deletion of N17 leads to extreme neurotoxicity and rapid neurological decline. These features typify the onset and progression of HD. The in vivo studies taken together with our recent findings, lead to the proposal that soluble spherical aggregates, which are stabilized by C38, might be the source of neurotoxicity in HD. In this competitive renewal application, we will pursue a unique approach that combines novel multiscale computer simulations with in vitro biophysical experiments to advance our understanding of the aggregation mechanisms and phase behavior of Htt-NTFs. Our studies are aided by our new methodologies for coarse-grained simulations. These simulations combined with novel in vitro experiments will help us understand how the C38 module stabilizes soluble spherical aggregates while slowing the conversion from soluble spheres to insoluble fibrils in Htt-NTFs that lack the N17 module. We also seek to understand how the fibril stabilizing effect of the N17 module competes with the fibril destabilizing effects of C38 in exon 1 spanning Htt-NTFs with polyQ tracts of different lengths. A clear understanding of the aggregation mechanisms and the structures that form as the result of the interplay among polyQ length, the flanking sequence modules N17 and C38 is absolutely necessary to discern the connection between Htt-NTF aggregation and neurotoxicity.

Lay Summary

PUBLIC HEALTH RELEVANCE: The interplay between flanking sequence modules and polyglutamine expansions within N-terminal fragments of the huntingtin protein controls the aggregation and neurotoxicity that gives rise to Huntington’s disease (HD), which is a devastating neurodegenerative disorder. Our studies will focus on the molecular mechanisms that give rise to specific species that are implicated as the sources of neurotoxicity in HD. These studies are crucial for the identification of drug targets for HD.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Huntington's disease

Years:
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