Mechanisms controlling sequestration and detoxification of Huntingtin proteins in yeast (Saccharomyces cerevisiae)

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Mechanisms controlling sequestration and detoxification of Huntingtin proteins in yeast (Saccharomyces cerevisiae)

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4

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Research Abstract

Huntington’s Disease (HD) is a neurological proteopathy caused by polyglutamine expansions in exon-1 of mutated Huntingtin (mHtt) proteins. The toxicity of the aggregation-prone mHtts (mHtt103QP) is suggested to be moderated in both neurons and yeast cells by their sequestration into inclusion bodies (IB). However, the exact pathways governing the sequestration and toxicity of mHtts are not fully understood. The overall aim of this project is to

reveal regulatory mechanisms implicated in the sequestration and detoxification of Huntingtin proteins. A yeast genome-wide imaging-based screening approach has been developed during the previous VR project period. Novel factors have been identified from the screen and will be confirmed and evaluated in humanized yeast model system. From our preliminary screening results, we found that the ribosome quality control complex (RQC) components, Ltn1 (Listerin E3 ubiquitin ligase), and its partner Rqc1, are key factors required for IB formation, ubiquitination, and detoxification of the Huntingtin protein mHtt103QP. Whether Ltn1 regulating the proteotoxicity of mHtt through altering the interaction between mHtt103QP and actin cytoskeletal structures will be elucidated. Further in-depth study of the relationship between RQC components and mHtt103QP management will provide us vital clues leading to diagnosis and therapeutics that prevent or treat the disease.

Further information available at:

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