The role of acetylation in regulating pathophysiology of tau

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Principal Investigators

PETRUCELLI, LEONARD

Institution

MAYO CLINIC JACKSONVILLE

Contact information of lead PI
Country

USA

Title of project or programme

The role of acetylation in regulating pathophysiology of tau

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01/09/2014

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

HDAC6 gene, tau Proteins, Acetylation, Cytoplasmic Granules, Tauopathies

Research Abstract
DESCRIPTION (provided by applicant): We seek to define the molecular mechanisms by which histone deacetylase 6 (HDAC6) and stress granules (SGs) interactively drive the pathophysiology of tauopathies, such as Frontotemporal Dementia. In so doing, we will test the

hypothesis that loss of HDAC6 activity augments site-specific tau acetylation, preventing the pathological recruitment of tau to stress granules, and slowing disease progression. We recently reported that HDAC6-mediated deacetylation of tau enhances accumulation and aggregation, and we have now identified the acetylation sites on tau that are regulated by HDAC6. We also recently reported that tau pathology develops in concert with SG pathology in human and mouse models. Understanding the role of HDAC6 in regulating tau acquires added significance because HDAC6 regulates SGs, which are protein/RNA complexes that form in response to translational inhibition. Thus, HDAC6 functions as a nexus, linking acetylation of tau, SG formation and disease progression. The work in this proposal will elucidate the mechanisms by which HDAC6 regulates tau recruitment to SGs, with a particular focus on tau acetylation, and also assess whether decreasing HDAC6 expression with antisense oligonucleotides (ASOs) is sufficient to alleviate both tau and SG pathology. We have already identified ASOs targeting HDAC6 that effectively decrease expression in mouse primary neurons, and through an active collaboration with Isis Pharmaceuticals, are working to identify ASOs that will progress to in vivo testing. Given HDAC6 inhibition or knockout produces no obvious toxicity in cells or in mice, HDAC6 as a therapeutic target possesses strong translational appeal. Our proposal is structured to provide a greater understanding of the intricate and dynamic relationship between HDAC6 and tau, as well as elucidate the role of HDAC6 and tau acetylation in SG dynamics. We will generate acetyl tau antibodies on HDAC6-responsive sites to investigate how acetylation on these key sites affects tau biology and SG dynamics in our cell culture and rTg4510 mouse models as well as postmortem brain tissue from tauopathy cases (Aim 1). We will also determine whether modulation of HDAC6, through the use of ASOs, diminishes tauopathy and preserves cognition in vivo (Aim 2). Using mouse primary neurons, fibroblast-derived neurons from human tauopathy patients, which we show exhibit robust SG formation in response to stress, and rTg4510 mice treated with HDAC6 ASOs, we will further determine the roles of HDAC6, tau and acetylation in regulating stress granule dynamics (Aim 3). Completion of these studies in tandem will fundamentally expand our knowledge of the pathophysiology of tauopathies, and provide key insights into the pre-clinical efficacy of HDAC6 ASOs as a novel therapeutic strategy.

Lay Summary

PUBLIC HEALTH RELEVANCE: We seek to understand how the enzyme histone deacetylase 6 (HDAC6) and stress granules, which are protein/RNA complexes, drive disease progression in dementia. We aim to therapeutically tamp down HDAC6 to modulate two competing cellular processes, acetylation and phosphorylation, at specific cellular sites on the tau protein, thereby decreasing the harmful aggregation of tau and the neuronal response to stress. We will test whether treatment with antisense oligonucleotides (ASOs) diminishes disease progression in cell models and preserves cognition in mouse models, thereby providing key insights into the pre-clinical efficacy of HDAC6 ASOs as a novel therapeutic strategy.

Further information available at:

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United States of America

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