Neurodegeneration Starts at the Nuclear Pore: Insights and Therapy for ALS and Dementia

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Online Webinar

For Researchers

Speaker:

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Abstract

While the genetic underpinning and end stage pathological hallmarks of neurodegenerative diseases are increasingly well-defined, the cellular pathophysiology of disease initiation and/or propagation remains poorly understood especially in sporadic forms of these diseases. Altered nucleocytoplasmic transport (NCT) has recently emerged as a prominent pathomechanism underlying multiple neurodegenerative diseases including Amyotrophic Lateral Sclerosis (ALS), Alzheimer's Disease (AD)/Frontotemporal Dementia (FTD), and Huntington's Disease (HD). Nucleocytoplasmic transport, as well as genome organization and gene expression, are governed by the nuclear pore complex (NPC) and interactions between its individual nucleoporin (Nup) components and karyopherins. Recently, specific Nup abnormalities have been reported in sporadic and familial forms of neurodegeneration. It has been proposed that these alterations at least in part contribute to disrupted NCT in disease. Interestingly, the specific Nups and NCT proteins pathologically linked to different neurodegenerative disease appear to be partially distinct. Consistent with the notion that rare genetic mutations in some Nups have been described in cell-type specific diseases, these studies suggest that nuclear pore injury may 1) contribute to the cellular specificity of neurodegenerative disease and 2) could be an early initiator of pathophysiological cascades underlying neurodegenerative disease. In this review we will discuss Nup and NPC disruptions and their impact on cellular function and neurodegenerative disease pathophysiology.

1. Coyne, A.N., et al. **Nuclear accumulation of CHMP7 initiates nuclear pore complex injury and subsequent TDP-43 dysfunction in sporadic and familial ALS.** Sci Transl Med 13 (2021).
2. Coyne, A.N., et al. **G4C2 Repeat RNA Initiates a POM121-Mediated Reduction in Specific Nucleoporins in C9orf72 ALS/FTD.** Neuron 107, 1124-1140 e1111 (2020).
3. Zhang, K., et al. **Stress Granule Assembly Disrupts Nucleocytoplasmic Transport.** Cell 173, 958-971 e917 (2018).
4. Grima, J.C., et al. **Mutant Huntingtin Disrupts the Nuclear Pore Complex.** Neuron 94, 93-107 e106 (2017).
5. Eftekharzadeh, B., et al. **Tau Protein Disrupts Nucleocytoplasmic Transport in Alzheimer's Disease.** Neuron 99, 925-940 e927 (2018).
6.Zhang, K., et al. **The C9orf72 repeat expansion disrupts nucleocytoplasmic transport.** Nature 525, 56-61 (2015).

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