J Neurol Neurophysiol 2022, Volume 13

Structural insight into transmissive mutant huntingtin species correlative light and electron microscopy and cryo-electron tomography

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Aggregates of mutant huntingtin (mHTT) containing an expanded polyglutamine (polyQ) tract is hallmarks of Huntington's Disease (HD). Studies have shown that mHTT can spread between cells, leading to the propagation of misfolded protein pathology. However, the structure of transmissive mHTT species, and the molecular mechanisms underlying their transmission remain unknown. Using correlative light and electron microscopy (CLEM) and cryo-electron tomography (cryo-ET), we identified two types of aggregation-prone granules in conditioned medium from PC12 cells expressing a mHTT Nterminal fragment: densities enclosed by extracellular vesicles (EVs) and uncoated, amorphous meshworks of heterogeneous oligomers that co-localize with clusters of EVs. In vitro assays confifirmed that liposomes induce condensation of polyQ oligomers into higher-order assemblies, resembling the uncoated meshworks observed in PC12 conditioned medium. Our findings provide novel insights into formation and architecture of transmissive mHTT proteins, and highlight the potential role of EVs as both carriers and modulators of transmissive mHTT proteins.