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Super-resolution fluorescence imaging of intracellular mutant huntingtin protein reveals a population of fibrillar aggregates co-existing with compact perinuclear inclusion bodies

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Background

The identities of toxic aggregate species in Huntington's disease (HD) pathogenesis remain unclear. While polyQ-expanded mutant huntingtin (Htt) is known to accumulate in compact inclusion bodies inside neurons, this is widely thought to be a protective coping response that sequesters misfolded conformations or aggregated states of the mutated protein.

Materials and methods, results

To define the spatial distributions of fluorescently-labeled Htt-exon1 species in the cell model PC12m (terminally differentiated into sympathetic-neuron-like cells with nerve growth factor), we employed highly sensitive single-molecule-based and stimulated emission depletion (STED) super-resolution fluorescence imaging modalities. In addition to inclusion bodies and the diffuse pool of monomers and oligomers, fibrillar aggregates ~100 nm in diameter and up to ~1-2 μm in length were observed for pathogenic polyQ tracts (expression experiments with 46 and 97 repeats) after targeted photo-bleaching of the inclusion bodies [1]. These short structures bear a striking resemblance to fibers described *in vitro* [2]. We identified a sharp cut-off behavior of maximum fibril length and documented the ensuing bundling of these fibers into denser arrangements of varying complexity, both in the cytosolic space and inside the neuritic processes.

Conclusions

Definition of the diverse Htt structures in cells will provide an avenue to link the impact of pharmacological agents to aggregate populations and morphologies. The latest observations w.r.t. co-localization of Htt with various quality control proteins such as the chaperone Hsp70 will be presented.

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