Protein aggregation in cells and machinery for disaggregation

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Protein misfolding and aggregation cause late onset, degenerative diseases, in which the misfolded protein or peptide can assemble into amyloid fibrils whose formation is associated with cell death. We use correlative fluorescence and 3D electron microscopy to study protein aggregation in models of Huntington's disease. Two different cytosolic disaggregase systems work in cooperation with the abundant and ubiquitous Hsp70 chaperone. In bacteria, fungi and plants, the Hsp100 AAA+ ATPases, including bacterial ClpB and yeast Hsp104, disassemble aggregates and prion fibrils. We have studied the threading action of ClpB by single particle cryo EM. In metazoa, disaggregation activity is provided by the combination of Hsp70 with an Hsp40 co factor and the nucleotide exchange factor Hsp110. We are examining the mammalian Hsp70 chaperone machinery, as it disassembles model amyloid fibrils, by atomic force microscopy and cryo EM.