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Cryo EM studies of protein aggregation and disaggregation

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Correlative fluorescence and 3D electron microscopy methods are being used to study models of protein misfolding and aggregation in cellular models of amyloid disease. Using electron tomography of yeast models, we are examining the structure of several different amyloid deposits in situ. The deposition of aggregates is the outcome of protein aggregation and its reversal by disaggregases. There are two known cytosolic disaggregases, both operating with the abundant and ubiquitous Hsp70 chaperone system. In bacteria, fungi and plants, the Hsp100 AAA+ ATPases such as bacterial ClpB and yeast Hsp104 disassemble aggregates and prion fibrils. We are using single particle EM to capture the threading of a substrate protein through the hexameric ring of ClpB. In metazoa, disaggregation activity is provided by the combination of Hsp70 with an Hsp40 co factor and one specific nucleotide exchange factor, the Hsp70 homologue Hsp110. By electron tomography and subtomogram averaging, we are also imaging the reconstituted mammalian Hsp70 chaperone machinery as it disassembles model amyloid fibrils.
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