Unravelling the structure of toxic protein aggregates in situ

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Protein aggregation is a hallmark of many neurodegenerative diseases, including Huntington's, Parkinson's and amyotrophic lateral sclerosis. However, the mechanisms linking aggregation to neurotoxicity remain poorly understood, partly because only limited information is available on the native structure of protein aggregates inside cells. We are addressing this challenge utilizing the latest developments in cryo-electron tomography (cryo-ET). We prepare thin lamellas of vitrified cells containing protein aggregates using cryo-focused ion beam, and subsequently image them in three dimensions by cryo-ET. This allows us to analyse aggregate structure within pristinely preserved cellular environments and at molecular resolution. Here I will discuss how our latest results shed new light into the cellular mechanisms of neurodegeneration.