Meng Lu's oral presentation for ICTP conference

Title:

Live-cell super-resolution microscopy reveals a primary role for diffusion in polyglutamine aggresome assembly

Abstract:

The mechanisms leading to self-assembly of misfolded proteins into amyloid aggregates have been studied extensively in the test tube under well controlled conditions. However, to what extent these processes are representative of those in the cellular environment remains unclear. Using super-resolution imaging of live cells, we show that an amyloidogenic polyglutamine-containing protein first forms small, amorphous aggregate clusters in the cytosol, chiefly by diffusion. The dynamic interaction among these clusters limits their elongation and leads to structures with a branched morphology, which differ from the predominantly linear fibrils observed *in vitro*. A proportion of these clusters then assemble via active transport at the microtubule organising center to initiate the formation of perinuclear aggresomes. Although it is widely believed that aggresome formation is entirely governed by active transport along microtubules, we demonstrate, using a combined approach of advanced imaging and mathematical modeling, that diffusion becomes the principal mechanism driving aggresome expansion. The increasing surface area of the expanding aggresome increases the rate of accretion due to diffusion of cytosolic aggregates, and this pathway soon dominates the aggresome assembly process. In extreme cases, this is sufficient to clear the cytoplasm of peripheral clusters. We also show that aggresomes mature over time, becoming more compacted as the structure grows. The presence of large perinuclear aggregates profoundly affects the behaviour and health of the cell and here we show via super-resolution imaging that aggresome formation and development are governed by highly dynamic processes that are important in the design of potential therapeutic strategies. (250 words)