Non-classical nucleation of tumor suppressor p53 fibrils hosted by mesoscopic protein-rich clusters

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About half of human cancers are associated with mutations of the tumor suppressor p53. Mutated p53 emerges as a powerful oncogene, which blocks the activity of wild-type p53 and several distinct anticancer pathways. The gained functions of the mutant have been related to the aggregation behaviors of wild-type and mutant p53. The thermodynamic and kinetic mechanisms of p53 aggregation are poorly understood. Here we employ time-resolved in situ optical, fluorescent, and scattering approaches and find that wild-type p53 forms an abnormal phase, mesoscopic clusters. The clusters exhibit several behaviors beyond the scope of classical phase transition theories: their size, ca. 100 nm, is independent of the p53 and crowder concentrations and decoupled from the protein mass held in the cluster phase. Thermodynamic analyses assuming a distinct composition of the cluster phase elucidate another unusual cluster property: the lack of solubility. We show that the cluster dynamics are fast and reversible, with a characteristic time of minutes, suggesting that the enhanced cluster formation might represent a p53 regulation pathway to fast storage and release. The nucleation of p53 fibrils deviates from the accepted mechanism of sequential association of single solute molecule. We find the mesoscopic clusters serve as a pre-assembled precursor of high p53 concentration that facilitate fibril assembly. Fibril nucleation hosted by precursors represents a novel biological pathway, which awards unexplored avenues to suppression of protein fibrillation in aggregation diseases.

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