Toward a comprehensive understanding of protein folding and misfolding

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Amyloid fibrils are associated with over 20 degenerative diseases including Alzheimer's disease, and dialysis-related amyloidosis. To study amyloid fibrils, we developed two types of unique techniques. First, to visualize amyloid fibrils, we combined total internal reflection fluorescence microscopy (TIRFM) with amyloid-specific thioflavin T (ThT) fluorescence [1]. With this approach, we succeeded in observing the growth of amyloid fibrils in real-time at a single fibrillar level for various amyloidogenic proteins including Aβ peptide.

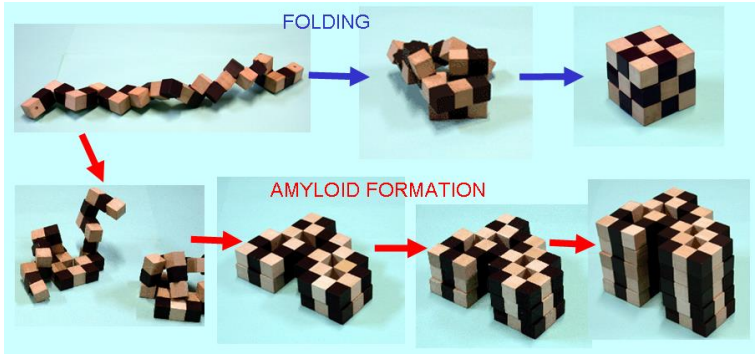

Fig. 1. Models of protein folding and misfolding.

Second, we present that ultrasonication is one of the best means of accelerating amyloid nucleation and thus the formation of fibrils [2, 3]. Combining the use of ultrasonication and a microplate reader, we propose an efficient approach to study the potential of proteins to form amyloid fibrils [4]. The results indicate that the solutions of denatured proteins are often supersaturated above the solubility limit and ultrasonic agitations release the supersaturation effectively, excluding solvated monomers to form fibrils.

With these techniques, we compare the mechanisms of protein folding and misfolding. We propose a general view of how the structures of protein and peptide precipitates vary dramatically from single crystals to amyloid fibrils and amorphous aggregates, in which "solubility" and "supersaturation" play critical roles [3].

References

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[3] Yoshimura, Y. et al. *Proc. Natl. Acad. Sci. USA*, **109,** 14446-14451 (2012).

[4] So, M. et al. *J. Mol. Biol.* **412**, 568-577 (2011).