Chaperone-Mediated Entropic Separation of Amyloid Nanofilaments

Miguel Rubi[1]

[1]University of Barcelona, Barcelona, Spain

The disassembly of misfolded protein aggregates is a requirement for the proper functioning of cells. It has implications in multiple neuropathologies, such as Alzheimer's and Parkinson's diseases. The active unbundling of fibrillar aggregates has recently been identified as a key rate-limiting step in the disassembly process. However, the nature of the underlying molecular mechanism remains an outstanding question. Here, we develop a coarse-grained computational approach from the atomistic structural information and show that the interactions of molecules tethered to fibrils lead to entropic forces consistent with the unbundling process observed in amyloid -synuclein disaggregation by Hsp70. We uncover two main types of entropic effects, categorized as intraprotofilament and interprotofilament, which are differentially affected by the system parameters and conditions. Our results show that only highly efficient chaperone systems can overcome the free-energy cost of the lateral association between two protofilaments. Through the analysis of cryoelectron tomography and high-speed atomic force microscopy data, we find that the conditions for highly efficient entropic force generation are those typically achieved with cochaperone networks and ATP hydrolysis, which require energy expenditure but do not provide an enthalpic component to the separation force. We highlight the implications of these results for the design of targeted therapies for the underlying neuropathologies.