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TITLE

AFM nanoprobing of alpha-synuclein self-assembly

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National Self-assembly of proteins into nanoaggeragtes defines the molecular mechanism of the development of such neurodegenerative diseases as Alzheimer's and Parkinson's disease (PD). Alpha-synuclein (α-Syn), misfolding and nanoassembly of which tightly linked to the development of PD, is a 140 aa long presynaptic protein which belongs to a group of natively unfolded proteins. The nanoaggregation rate of α-Syn is accelerated by various factors such as low pH, biogenic polyamines and single point mutations (A30P, E46K, and A53T) which correlate with early-onset familial PD. Unraveling the effects of these factors on misfolding of α-Syn is important for understanding the molecular basis of the disease development. The main challenge in studying misfolding phenomenon is the existence of transiently populated misfolded conformations that lead to pathological aggregation of a protein. Strong correlation between the strength of interprotein interactions and the propensity of a protein to aggregate makes force spectroscopy a unique tool for studying misfolding of a protein. Using this approach we probed pair-wise interactions between individual α-Syn molecules at conditions that induce conformational transitions associated with enhanced aggregation. Particularly, we focused on the effect of cellular polyamine-spermidine on α-Syn misfolding and self-assembly. We show that at conditions close to physiological, addition of spermidine results in dramatic increase of the protein's propensity to misfold. Force spectroscopy approach not only enabled us to detect misfolded pathological conformations which are responsible for the first step of aggregation – dimer formation but also allowed us to characterize these misfolded states. Our results demonstrate that misfolding of α-Syn is characterized by a set of conformations and mutations change the misfolding pattern as well as the strength of intermolecular interactions. Despite marked differences and heterogeneous nature of interacting misfolded conformers α-Syn variants have common interaction sites as determined from force spectroscopy analysis. These sites are mostly localized within NAC region of α-Syn molecule known to be responsible for α-Syn aggregation. Additionally, we found that regions outside NAC (within C-terminus) play an important role in α-Syn misfolding and dimerization.

Biography

Dr. Krasnoslobodtsev has completed his Ph.D. from New Mexico State University and postdoctoral studies from University of Nebraska Medical Center. He currently holds a Research Assistant Professor position at the Department of Pharmaceutical Sciences, University of Nebraska Medical Center. His research interests lie in the area of nanoimaging and protein misfolding diseases.