Solving the next step in the mystery of prions

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Working towards the ultimate goal to develop therapeutics to treat diseases such as Alzheimer's, Parkinson's, ALS, and BSE (Mad Cow Disease), University of Alberta scientists Michael Woodside, Hao Yu, and Derek Dee are investigating the physical principles underlying the formation of misfolded protein aggregates. The aggregates of misfolded proteins—proteins that clump together in the "wrong" structure—feature prominently in these fatal degenerative diseases.

"This is the big mystery we're trying to solve," says Woodside, a professor of physics. "We want to understand the physics of the conversion from 'good' proteins to 'bad.'" Understanding the conversion process should lead to finding new targets for drug development. Woodside's research group is one of the world leaders in the area of single-molecule studies of protein misfolding.

A couple of years ago, the UAlberta researchers examined a single prion protein molecule to study how it behaves in isolation. However, it is in the interaction between molecules which is important in disease. To further the journey along the road to the eventual development of possible treatments, Woodside and his colleagues have now studied the interaction of two molecules. In contrast to single isolated molecules, in which incorrect structures did not last very long, two molecules interacting together could form an incorrect structure that was more stable than the correct one. The group used sensitive laser tweezers to manipulate the proteins and observe the microscopic motions of the molecules as they changed shape.

Their most recent discovery opens a new window onto the microscopic mechanisms governing protein misfolding. Says Woodside, "Our work is best viewed as just one step in solving a big mystery that still endures almost 20 years after the Nobel Prize was awarded for the prion hypothesis."

More information: Protein misfolding occurs by slow diffusion across multiple barriers in a rough energy landscape, Hao Yu, DOI: 10.1073/pnas.1419197112

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