

Computation and theory to predict structures and mechanisms for protein misfolding in amyotrophic lateral sclerosis

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Research Abstract

As we age, we begin to face an onslaught of threats to our health that evolution has not protected us against. Many of these include degenerative diseases such as Alzheimer's disease, Parkinson's disease, and Lou Gehrig's disease or ALS. It is up to us to design strategies for slowing, stopping, or reversing the progression of these currently incurable diseases. To do this involves understanding the causes of the disease, which are due

fundamentally to proteins behaving badly. Here we will investigate the molecular origins of how proteins malfunction in ALS, a neurodegenerative disease, to elucidate at the atomic level what may be going wrong in the cell. Malfunction often involves proteins that have misfolded, and as a consequence have aggregated together. Misfolding may be exacerbated by oxidative damage to proteins, which generally occurs as a natural consequence of aging. Most cases of ALS strike sporadically, with no known hereditary link, with the likelihood increasing as we age. What goes wrong in the cell? We will focus on how oxidative damage may be a cause of sporadic ALS. We will investigate how oxidative damage may destabilize proteins and render them susceptible to misfolding. We have previously developed a computational method that is capable of predicting how long a patient will live once diagnosed with ALS, given they have an inherited form of the disease. We propose here to extend our computational method to the much more prevalent sporadic form of the disease, by investigating the role of oxidative damage in the aging brain. We have previously developed a novel computational method that allows misfolded protein to be specifically targeted. Developing and applying our methods to describe the mechanisms and consequences of protein misfolding in ALS will allow us to rationally predict critical protein targets that may stop the progression of this currently fatal, misfolding-related degenerative disease.

Further information available at:

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