How damaging proteins form

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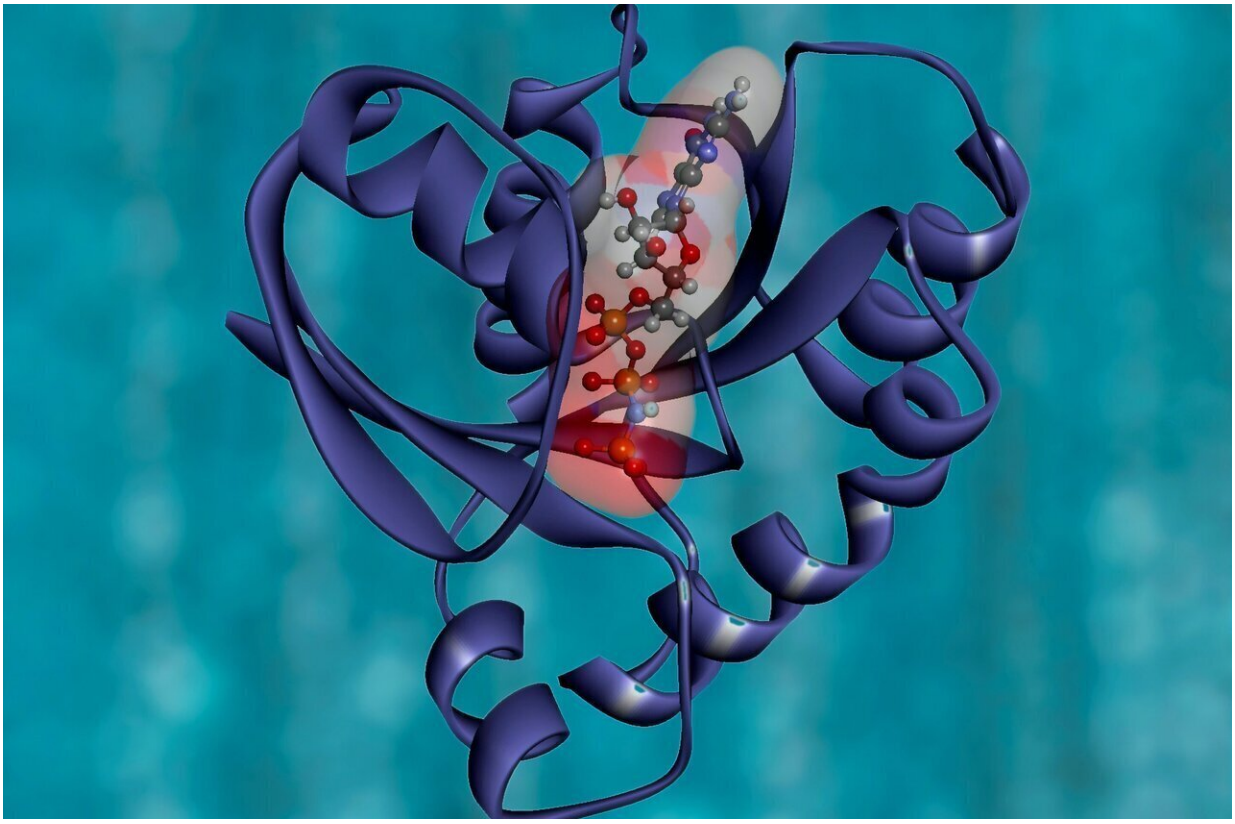

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Alzheimer's disease and Parkinson's disease are both examples of amyloid diseases, where malfunctioning proteins accumulate to form fibrils and larger aggregates called amyloid plaques. In the journal *Biophysical Chemistry* researchers at the University of Leeds, UK, review progress in methods for studying crucial but fleeting intermediates in the

formation of these fibrils.

Amyloid plaques accumulate in the space outside and between brain cells in degenerative brain diseases. Recent evidence suggests the plaques can also occur inside cells. While best known for the link with degenerative diseases of the brain, amyloid is also implicated in diseases of other organs, including damage to the pancreas in type 2 diabetes and the joints in dialysis-related amyloidosis.

Potent precursors

The damaging forms of amyloid are believed to originate from normal proteins that become misfolded in ways that allow them to aggregate into the persistent fibrils and plaques. The fibrils assemble from smaller clusters of protein called oligomers, but these exist only briefly before aggregating further, making them difficult to study.

"These fleeting oligomer intermediates are considered to be key contributors to the onset of amyloid disease," says Sheena Radford of Leeds University's Astbury Centre for Structural Molecular Biology, a corresponding author of the review. Researchers are therefore keen to find ways to study the oligomers.

The review was written for a Special Issue of Biophysical Chemistry celebrating the life of Professor Sir Christopher Dobson, a major pioneer in the amyloid field who died in 2019. "Chris was my post-doctoral mentor," says Radford, "so myself and my co-authors were delighted to be able to contribute to the Special Issue."

Methods and insights emerging

One challenge in understanding the oligomers is to identify them within

complex molecular mixtures. The authors review several main methods. For example, nuclear magnetic resonance spectroscopy detects the molecules using the radio-wave signals they can absorb when placed in a strong magnetic field. Fluorescence spectroscopy reveals fluorescent dyes that can be selectively attached to individual molecules of interest. Other highly specialized procedures can similarly detect the presence of single molecules.

In a second major strategy, a variety of chemical and biological interventions can be used to encourage specific oligomers to form in unusually large quantities, enabling the purification of samples for detailed study. The methods mentioned here are key examples of the wide range of techniques that are increasingly opening up the world of amyloid-forming oligomers to researchers' scrutiny.

The review article is focused largely on the methods for undertaking that scrutiny, rather than the results they are revealing. In general, however, the authors emphasize that significant insights into both the precise structures and the biological functions and toxic effects of the oligomers are emerging. "We hope that the techniques we review will improve basic understanding of protein aggregation to open the way to better designed therapies for amyloid disease," says Andrew Wilson, the second corresponding author, emphasizing the ultimate clinical goal.

Radford points out that while the most prominent amyloid disease, Alzheimer's, was first classified more than a century ago, techniques to study amyloid in atomic detail have only emerged in the past five years or so. The relatively young research effort exploiting the techniques reviewed in this article can be expected to yield many more key insights soon.

More information: Emma E. Cawood et al. Visualizing and trapping transient oligomers in amyloid assembly pathways, *Biophysical Chemistry*

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