Peptide Self-Assembly – Threats and Opportunities

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Country

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Title of project/programme

Peptide Self-Assembly - Threats and Opportunities

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01/01/16

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10.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

peptide self-assembly | amyloid | biocompatible materials | neurodegenerative disease | aggregation mechanism

Research Abstract

We aim to explore the full complexity of peptide and protein aggregation with an over-arching goal to combat its threats and harness its opportunities. We focus on a small set of peptides: a hydrogel peptide (HP), A? from Alzheimers's disease and ?-synuclein from Parkinson's disease. These have distinct sequence, size and aggregation propensity, but similarities in terms of underlying mechanism, molecular driving forces and final structures to provide both specific and general insights regarding the reaction pathways and controlling factors. We will investigate

*The aggregation mechanism of HP and its connection with materials properties in terms of mechanical performance, gel stability and rate of disruption, and how all these properties depend on extrinsic factors. The results may underlie future biomedical applications, e.g. for slow release of drug compounds.. *The aggregation mechanism of HP, A? and ?-syn in body fluids and intracellular environments. *Aggregation mechanisms in sequence variant mixtures. *The mechanism of formation of on path-way oligomers as they form and transform during the aggregation reactions of HP, A? and ?-syn. We aim at a quantitative description of the size distribution as a function of time, the rates of inter-conversion and the reaction order for each microscopic step involving the oligomers. Which conditions and components modulate the rate constants. What is the role of fibril surface properties in secondary nucleation? *Structure of aggregates and co-aggregates. How are peptide variants organized relative to one another in co-aggregates? Are other components from complex solutions incorporated in the aggregates? *Full aggregation reaction network and energy barriers of each microscopic step including its enthalpic and entropic contribution. *Early diagnostics. Can our aggregation assays provide diagnostic power to discriminate AD or PD patients from healthy controls at early stages of the diseases using samples of any body fluid? Will fractionation improve discrimination? *Structure and surface character of oligomers. Do oligomers have distinct surface character and interaction partners compared to monomer and full-length fibrils? Or is the higher toxicity of oligomers a result of their higher diffusion rate? *Novel materials-forming peptides. Methodology: The most important aspect for all our studies is careful experimental design and sample preparation and selective labeling with various isotopes. We have developed highly efficient expression and purification systems for A? and ?-syn. We use mainly bulk methods such as ThT fluorescence, CD and NMR spectroscopy, dynamic light scattering, neutron scattering with contrast variation, small angle X-ray scattering, rheology measurements, confocal and super-resolution microscopy, mass spectrometry (MS), NMR spectroscopy, SPR, QCM, other surface techniques, mutational analysis, protein arrays. We develop methodology for accurate determination of very low peptide concentration, for various forms of rapid separation by size or charge in microfluidics. We build an oligomer generator with immobilized fibrils and monomers in constant flow over these fibrils to address the size of the detaching species and to study the influence of various contributing factors to oligomer formation. The results may lead to future development of biocompatible materials, as well as earlier diagnosis and new routes for intervention with protein aggregation diseases. It brings an absolutely unique angle by pioneering a physical chemistry view of aggregation, showing that aggregation is a fundamentally physical phenomenon that can be understood using a regular chemical kinetics framework. Building on this we propose several innovative and high risk direction, in particular the ambitions to find mechanism of oligomer formation and reformation, origin of toxicity, novel tools for early diagnostics and novel self-assembling peptides for future biocompatible materials.

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