LINKING PROTEIN-PROTEIN INTERACTIONS TO THE DIVERSITY OF AMYLOID-LIKE AGGREGATES

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Key Words: Protein-Protein Interactions, Amyloid Aggregates, Sub-visible Particles, Polymorphism

Protein aggregation is often studied in the context of neurodegenerative diseases. Deposits of supramolecular aggregates, often appearing as ordered fibrils, are associated with the onset of devastating pathologies as Alzheimer´s and Parkinson´s diseases. Equally important is the impact that the formation of protein aggregates may have in the quality of a protein drug product. The presence of the so-called sub-visible particles (SVP) and visible particles in protein drug product is indeed considered one of the risk factors potentially inducing immune response in patients. Finally yet importantly, protein aggregates, and particularly amyloid fibrils, have unique structural, physico-chemical, mechanical and optical properties, making them appealing bio-inspired materials for several applications. Either one looks at protein aggregation in the context of diseases, drug development or biomaterials, understanding how protein-protein (PPIs) and protein-solvent interactions (PSI) determine aggregation kinetics and the morphology/structures of the final aggregates is a *conditio sine qua non* for unraveling the molecular mechanisms ruling the self-assembly reaction and for controlling it.

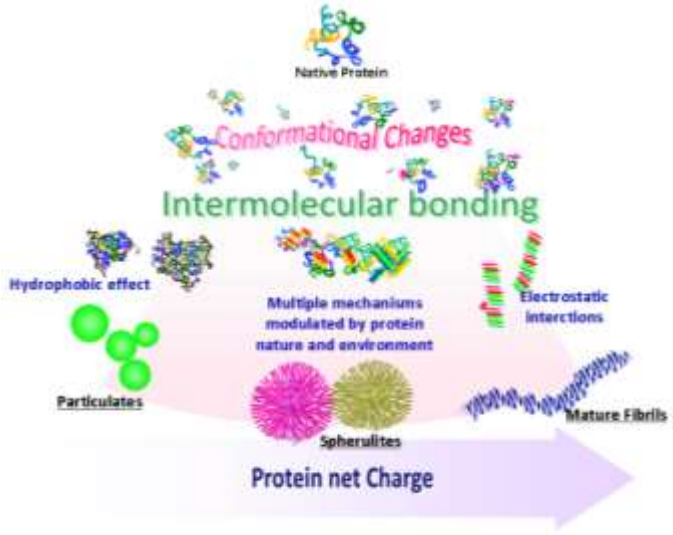

Figure 1 – Scheme representing the interplay between possible interactions and mechanisms during a protein aggregation process. In specific conditions, the formation of different morphologies and 3D arrangements of the final aggregates can occur [1].

In our group, we have reported the possibility for a large group of proteins under specific destabilizing conditions to form a variety of protein aggregates, being it not limited to the formation of amyloid fibrils (Figure 1) [1]. In line with the scope of the conference, I will present our unique approach based on advanced fluorescence microscopy, small angle X-ray scattering and spectroscopy and aimed at identifying the key PPIs and PSIs responsible for such variability in structures and morphologies [2-6]. We use surfactants, salts, alcohols in bulk and microfluidic setups to finely tune the interactions between proteins and, consequently, control the self-assembly process. Our results show that subtle changes in the PPIs and PSI do not only affect the kinetics, but they may also have a dramatic effect on the 3D arrangement, microscopic structures, mechanical properties and stability of the final self-assembled structures. Our findings provide a scenario in which a pool of highly heterogeneous structures can be generated as a result of interconnected aggregation pathways, being this aspect of key relevance especially for protein drug product development and optimization.

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