Exploiting homomers to reveal new principles of protein interaction, polymerization and aggregation

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Principal Investigators
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Research Abstract

In the protein universe, 30 to 50% of proteins self-assemble to form symmetrical complexes consisting of multiple copies of themselves, called homomers. A peculiarity of homomers is that any mutation is necessarily repeated in all subunits. In a symmetric dimer for example, any mutation of one copy is also found in the second identical copy. Depending where the mutation occurs on the surface, the repetitions of the mutation may or may not be “synergistic”, i.e., participate together to the formation of a new self-interaction. We propose that the consequences of a mutation depend mainly on two factors: (i) its location on the homomer’s surface, which influences its synergy and (ii) the symmetry type of the homomer. We anticipate that these two factors are tightly coupled to the probability that a random mutation triggers the infinite polymerization and aggregation of a homomer. We thus propose a two-pronged

approach to analyze this question. (i) In silico, using homomers of known three-dimensional structure, we will infer a “risk factor” for every surface residue, reflecting its probability to be associated with polymerization. We anticipate that high-risk residues are, together with their environment, under pressure to avoid un-wanted interactions. We also anticipate those sites to be under stronger evolutionary constraints. (ii) In vivo, we will artificially introduce amino acid substitutions in homomers at sites that are at high or low-risk, and quantify the potential of these mutations to trigger aggregation or polymerization of the homomer. This project, which combines both theoretical and experimental biology, will help us unveil new basic physico-chemical properties of proteins and of their potential to form unwanted aggregates in cells. This knowledge will contribute to our better understanding of important diseases involving uncontrolled self-association of proteins, such as Parkinson’s, Alzheimer’s, Huntingdon’s, or the sickle cell disease.

Further information available at:

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