Oral presentation

Competition between protein aggregation and protein complex formation

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Background

Interactions between proteins are vital for essentially every process in a living cell. Physico-chemical complementarity, which can be considered as the driving force for molecular recognition, has been found to not consistently explain protein-ligand interactions. As aberrant interactions should be avoided in order to maintain cell viability, promoting complex formation and preventing protein aggregation are two opposite requirements on the physico-chemical properties of protein surfaces.

Methods

As a first step, aggregation propensity profiles were calculated using the Zyggregator algorithm [1-3], which takes hydrophobicity, charge, structural propensities and alternating hydrophobic-polar patterns into account. Positive peaks in these profiles indicate regions that promote aggregation while negative peaks identify regions preventing aggregation. These calculations are based on individual aggregation propensities for each amino acid based on their physico-chemical properties and experimentally determined [1-3]. The aggregation propensity profiles were then mapped onto the structures of protein complexes [4] and aggregation propensity patches of interfaces and surfaces were compared.

Results

We found that interface regions of the analysed protein complexes are on average more aggregation prone than other surface regions (see Figure 1). The aggregation propensity is more effective than hydrophobicity for identifying such interfaces. Our results indicate that the determinants of protein complex formation are similar to those of protein aggregation. We further show that the competition between these two processes is mediated by the presence of disulphide bonds and salt bridges, which have evolved as negative design principles to prevent interfaces from triggering uncontrolled aggregation (see Figure 1).

Conclusion

The specificity in molecular recognition is achieved through a combination of positive and negative design principles, which, respectively, promote the assembly of functional complexes and prevent the formation of potentially dangerous aggregates.
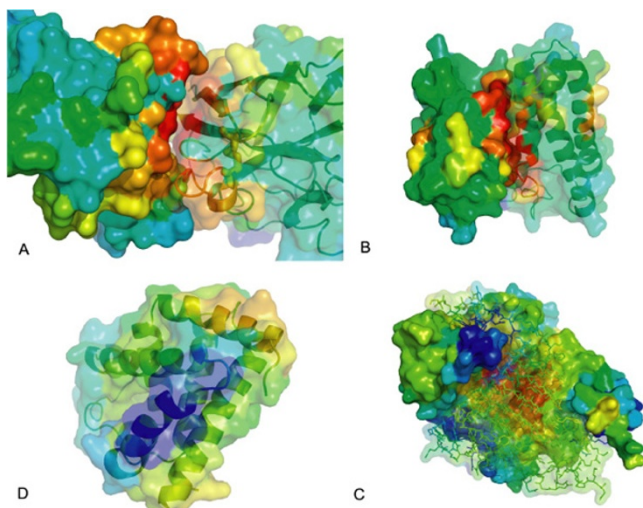
Figure 1
Protein aggregation propensity surfaces, red indicates aggregation prone regions and blue aggregation resistant regions. **A** The aggregation prone interface of the 'mainly-β' – homodimer complex (PDB structure: 1XSO) is stabilized by a disulphide-bond (in 'sticks' representation). **B** Aggregation prone interface of an 'mainly-α' homodimeric protein complex (1BBH). **C** Aggregation prone interface of a cyclic trimeric protein complex (1KRR). **D** Aggregation propensity surface of the aggregation resistant and monomeric human myoglobin protein (2MM1).

References
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