Modelling and Targeting Intrinsically Disordered Proteins Involved in Human Diseases

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Intrinsically disordered proteins (IDPs) are polypeptides containing long regions (more than 30 consecutive residues) that lack stable secondary structures (α-helix and β-strand). Bioinformatics analyses of several proteomes indicate that more than one third of eukaryotic proteins are intrinsically disordered. Many of them are involved in signalling pathways or regulation processes, and are considered as critical hubs in protein interaction networks (Uversky 2011). Overexpressions, mutations or dysfunctions of these proteins are involved in many human diseases, including cancer, diabetes, cardiovascular and neurodegenerative disorders (Uversky *et al*. 2009). Thus, a very promising route for the development of new drugs against these diseases was to develop drugs that could interfere with the protein-protein interactions involving IDPs.

IDPs can specifically interact with several proteins thanks to their intrinsically disordered region (IDR) which is highly flexible and capable of adopting various conformations to fit their partner binding sites. More specifically, many IDRs undergo a disorder-to-order transition upon binding, towards α-helical or β-strand conformations called Molecular Recognition Features (MoRFs) (Mohan *et al*. 2006). Depending on their sequence and environment, MoRFs either fold during the binding process (coupled folding and binding mechanism), or transiently pre-exist before interacting with their binding site (conformational selection mechanism) (Espinoza-Fonseca 2009).

Based on MoRFs identification in IDRs, different strategies can be used to design inhibitors of an IDP association. The first one is to design molecules that mimic the MoRF structure observed in the protein-protein complex but at the same time, be able to bind to the IDP partner with high affinity, in such way as to block the IDP binding (Cheng *et al*. 2006). A second one is to design molecules that directly bind to the IDP and stabilise a conformation different from the one recognised by its partner (Metallo 2010). Another strategy is to design molecules that tightly bind to the MoRF structure and hinder the recognition by the IDP partner. The first strategy needs the determination of the quaternary structure of the IDP-protein complex. The last two require characterising the unbound IDP conformations which are transiently adopted in solution.

However, IDPs are difficult to be structurally studied using experimental approaches due to their high flexibility and dynamics. Very often, the atomic coordinates of IDRs are absent from the Protein Data Bank crystallographic structures. The lack of a homogeneous conformation in solution also makes NMR approaches very demanding. Thus, providing a comprehensive description of IDP conformational ensembles is still a challenging task (Mittag & Forman-Kay 2007). In this context, computational tools are complementary approaches that can considerably help to elucidate the structural determinants of the IDP-protein interactions.

This presentation will address two IDPs under study in our group, the Aβ peptide involved in Alzheimer's disease (McLean *et al*. 1999) and the TCTP protein involved in the tumor reversion process that enables cancer cells to lose their malignant phenotype (Bommer, 2012). It will be shown how

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enhanced molecular dynamics simulations enable the exploration of the IDP ensemble of conformations and to detect those, rich in secondary structures that are prone to form protein assemblies (Tran et al. 2016). In the case of TCTP, a nascent collaboration with the Bioinformatics Institute of A*STAR in Singapore will help in identifying the proteins that bind its IDR, in the perspective to propose structural models of TCTP-protein complexes. All together, these theoretical studies can guide the design of new therapeutic molecules targeting and inhibiting IDPs.

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