Structural Biology, ASB/ABA meeting, Melbourne

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Structural biology plays a pivotal role in understanding complex molecular assemblies that encode vital functions in cellular processes. The determination of the nucleic acids, protein, and lipid membrane structures (Sani et al. 2012) allows to decipher how their interplay regulates important biological functions (Sani and Separovic 2016). Yet, it remains a significant challenge to study large biomolecules using standard biophysical tools, which stimulates the development of new techniques and approaches to tackle otherwise unfathomable large biomolecular systems. Size is not all: intrinsically disordered proteins (IDPs) are providing novel source of information for understanding biological processes. Recent studies have established that their lack of defined structure is not prohibiting function and, accordingly, IDPs are now investigated as potential therapeutic targets.

The Structural Biology session at the ABA/ASB meeting in Melbourne showed ideal archetypes of new biophysical methods to study dynamics in large proteins and how binding to IDPs can modulate key molecular mechanisms.

The research group of Professor I. Shimada has developed a novel NMR relaxation method to observe multiple quantum coherences relaxation of ¹³C-labeled side-chain methyls in high molecular weight proteins. This method allowed quantitative measurements of chemical exchange processes in the microsecond to millisecond timescales using differential multiple quantum relaxation rates and a heteronuclear double resonance NMR pulse technique. Conformational exchanges

occurring in the 200-kDa potassium channel KirBac1.1 were successfully determined, providing deeper understanding of the channel allosteric pathways (Toyama et al. 2016).

Matthews and co-workers have shown that unusual binding kinetics associated with intrinsically disordered regions (IDRs) involved in transcriptional complexes can modulate specification in neuronal cells. Using FRET-based spectroscopy, the protein-protein interactions tangled in the large LIM-homeodomain complexes and DNA-LIM interactions were investigated in motor neurons. Single disordered LIM interaction domains showed expected weak interactions but surprisingly slow dissociation kinetics within the large complexes, promoting an increase in DNA binding affinity. The study, presented by Professor J. Matthews, suggests that a single intrinsically disordered region could regulate the timing of transcriptional complex assembly by achieving highly disparate binding kinetics (Robertson et al. 2018).

Interestingly, IDPs were also investigated as potential targets to treat infectious diseases. Norton and co-workers have shown how disordered antigens can serve as targets for antibodies albeit with different molecular interactions than ordered antigens. Dr C. MacRaild revealed how the monoclonal antibody 6D8 interacted with a short epitope within the intrinsically disordered malaria antigen, MSP2. The multiple transient interactions, which were observed via NMR chemical shift perturbations, relaxation rates, paramagnetic relaxation enhancement, and molecular dynamic simulations, were modulated by topological features rather than sequence-specific interactions. Understanding the non-specific antigen-antibody interactions could enable the design of new vaccine formulations based on disordered antigens (Krishnarjuna et al. 2018).

The work presented during the meeting showcased the power of biophysical tools in resolving complicated molecular mechanisms in key biological molecules, despite their large size and disordered nature. The structural insights provided by structural biology studies remain an essential step to enable the development of novel approaches to treat disease states.

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Compliance with ethical standards

Conflict of interest Marc-Antoine Sani declares that he has no conflict of interest. Takayuki Nishizaka declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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