Conclusions and Outlook

Description

The relevance of carbohydrate-lectin interactions in controlling many physiological processes is key to various disciplines. However, the understanding of the molecular basis regulating such events is still limited. The main take-home message that we want to convey with this e-chapter is that the choice of a correct assay is fundamental for the study of binding interactions. One must be aware that the assay features strictly determine which sort of knowledge is acquired about the process under investigation. Each assay has its constitutive advantages and disadvantages; it is the responsibility of the operator to recognize them. We hope to have given the reader the tools to discriminate within the most conventional methods for sampling lectin-ligand interactions and to be critical about each different approach. We believe that our contribution will help early-stage researchers in taking suitable choices to develop their projects.

Given the fact that experimental results reflect the assay set-up, it is logical that the best way to achieve comprehensive learning goes through the application of multi-interdisciplinary approaches. To get the most precise picture of the phenomena under observation, it is advisable to employ a combination of various techniques which are becoming more and more available in the fields of structural and cell biology, medicinal and computational chemistry. For example, a complementary method to the determination of binding affinities is X-ray crystallography. Elucidating the molecular structure of the sugar-lectin complex, the X-ray diffraction pattern illustrates the mechanism of sugar recognition at the atomic level. (Fujimoto, 2014) Another example of a versatile technique to unravel such interactions in the dynamic of their formation is NMR spectroscopy. (Marchetti et al., 2016)

The ones we described in this chapter are traditional methods to access quantitative details about the carbohydrate-protein association. Regardless of their success, these methods have weaknesses, for their extensive labour, cost and time, that can interfere with the on-going studies. To overcome such shortcomings, significant advances have been done and are still evolving in improving these techniques. A lot of efforts are devoted to reducing sample amounts while achieving high sensitivities. New approaches have also emerged, securing high-throughput screening (e.g. glycan array technologies) (Fukui et al., 2002;Wang et al., 2002) or circumventing problems related to aggregation (e.g. bio-layer interferometry) (Laigre et al., 2018).

Additional resources in the study of biomolecular complexes are several computational methods, which are used to predict binding modes and understand carbohydrate specificity.82 As underlined in other publications, (Angioletti-Uberti et al., 2017; Tian et al., 2020; Tjandra & Thordarson, 2019) more work has to be done to combine computational modelling and theoretical studies, especially in the field of drug design in multivalency. The verification of theories by empirical results and their expansion to prediction models are of inestimable potential in biomedical research.

Most of the tools now available are dedicated to seeking the most potent binder within a pool of compounds. Another fundamental requirement for drug applicability is usually set aside: selectivity. Multivalent systems, such as glycodendrimer or glycosylated nanoparticles, lie at the interface between small-molecule and supramolecular chemistry. The concept of “super-selectivity” (i.e. the rapid increase in adsorption probability typical of multivalent particles, exclusively) was elaborated to appreciate the peculiar features of multivalent assemblies in a broad range of applications. (Martinez-Veracoechea & Frenkel, 2011; Curk et al., 2017) This revealed the importance of tuning ligand density,

(Di Iorio & Huskens, 2020) as in a “Velcro” effect for which it is more important to have many weak interactions than a few strong ones for selectivity. New paradigms in the multivalency field should guarantee the adaptation of old design principles to novel ones, which are different from the mere optimization of binding strength, typical for small drug candidates. More in general, it is essential to integrate the information on affinity and selectivity of lectin-sugar interactions with details on their kinetics. An in-depth analysis of binding kinetics, combined with pharmacodynamic/pharmacokinetic models, is essential to predict the time-course effect of the drug *in vivo*. (Tonge, 2018)
The simultaneous application of different biophysical approaches and theoretical predictions will be the key to successfully decipher the “glycocode” and develop therapeutics that make use of such language.

Category

1. News