

Yadav, S.; Naresh, K.; Jayaraman, N., 2021, "Surface density of ligands controls in-plane and aggregative modes of multivalent glycovesicle-lectin recognitions", *ChemBioChem*. In print. DOI: 10.1002/cbic.202100321.

Uncovering many finer details of the carbohydrate-protein interactions remains a pivotal goal in order to elucidate mechanisms of manifold biological functions. Sustained efforts have enabled to establish that this class of macromolecular interactions heavily rely on the multivalency, which brings with it logarithmic enhancements in binding affinities in comparison to monovalent interactions. The multitude of biological functions mediated by these interactions also provides a clue to the presence of mechanisms beyond the multivalent effect. Several synthetic multivalent ligands show that a commonly encountered mechanism is the kinetically driven multivalent ligand-lectin complexation leading to aggregation and cross-linking. The cellular carbohydrate-protein interactions are observed to operate in two distinct modes, namely, an intra-membrane cis-interaction and an inter-membrane trans-interaction, responsible for either an inhibitory or a productive activity, respectively. A strong sugar-density driven situation emerges in these interactions. In order to model such interactions at the cell membrane surfaces, the present study focusses on the synthetic glycovesicle surfaces and their interactions with carbohydrate-binding proteins, namely, lectins. A (1→3)(1→6)-linked mannose trisaccharide, which forms the core segment of oligomannose glycopeptides, is undertaken in the present study, in order to delineate the sugar-density dependent aggregation vs chelation modes of binding. Covalent polydiacetylene polymer vesicles incorporated with varying sugar densities are prepared and their lectin binding behavior analyzed by light scattering technique and atomic force microscopy. The binding affinities governing these modes of binding are elucidated with the aid of surface plasmon resonance technique. A major finding of the work is the evolution of a successful approach to predictably emerge the chelation mode of intra-vesicular ligand-lectin interaction. The approach establishes that the sugar density at the vesicle surface holds the key to permit chelation mode of binding, in addition to the aggregative mode of binding. These two modes are seen to exhibit similar order of sub-nanomolar to nanomolar binding affinities and within these affinities, the chelation mode preferred ~4 times higher binding affinity. The work thus uncovers for the first time an ability to model the biological cis-interaction. In the light of the intense interest in carbohydrate-protein interactions, the present study provides a definite clue to an elusive type of interaction, which has not been observed commonly.