Poster Presentation

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Structural basis of degenerate specificity of an anti-sugar antibody

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Although remarkable specificity of the acquired immune system was clearly being demonstrated, degenerate specificity in immune recognition is often been observed. We had started working on degenerate specificity of antibodies using peptide and sugar as a model system. Both carbohydrate antigen (me-α-Man) and peptide (DVFYPYPYASGS) were established to be equivalent in polyclonal as well as in mAb (2D10) responses (1). Thermodynamic analysis of Ag-Ab interactions had suggested the role of conformational flexibility (2) while crystallographic analysis indicated the importance of plasticity in the interactions (3) of the antigen combining site in the manifestation of molecular mimicry. It has been pointed out that even if the potential for flexibility existed, it was not being utilized while recognizing both ligands. So, in order to address this conundrum we started looking for other sugars and peptides that can bind to the mAb 2D10 with comparable affinities. Crystallographic analysis of 2D10 binding to five different sugars (me-α-Glc, α-Lac, α1-3-Mannobiose, α1-6-Mannobiose, α1-3, α1-6-Mannotriose) has given insights underlying the basis of specificity in molecular recognition. Comparison of all the structures has demonstrated that the antigen combining site for sugars is constituted of CDR H3, L1 and L3 only. All five sugars have an overlapping primary binding site (equivalent to me-α-Man interacting region). This primary sugar binding site has been shown to accommodate similar as well as dissimilar sugars by utilizing plasticity in the interacting residues available in the antigen combining site. The reducing sugar of the similar disaccharides (α1-3-Mannobiose, α1-6-Mannobiose) have been adjusted in the same direction but with utilizing different sets of interacting residues of the antibody paratope. However, the reducing sugar of a dissimilar disaccharide (α-Lac) exploits different paratope space altogether. The trisaccharide (α1-3, α1-6-Mannotriose) was accommodated in the same site by utilizing the conformational flexibility in the paratope region (mainly in CDR L1). This study had demonstrated that an affinity matured antibody may utilize at least three different strategies in order to accommodate structurally similar/dissimilar sugars.

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