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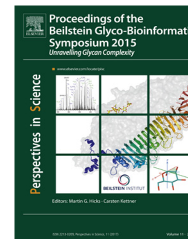

Complex carbohydrate recognition by proteins: Fundamental insights from bacteriophage cell adhesion systems☆

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Summary Protein—glycan interactions are ubiquitous in nature. Molecular description of complex formation and the underlying thermodynamics, however, are not well understood due to the lack of model systems. Bacteriophage tailspike proteins (TSP) possess binding sites for bacterial cell surfaces oligosaccharides. In this article we describe the analysis of TSP-oligosaccharide complexes. TSP provide large glycan interaction sites where affinity and specificity are guided by the protein surface solvation and the conformational space sampled by the respective glycan. Furthermore, we describe a computational approach to analyse the conformational space sampled by flexible glycans of bacterial origin, a prerequisite for a thorough understanding of TSP-oligosaccharide interactions.
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Abbreviations: TSP, tailspike protein; CBM, carbohydrate binding module; ITC, isothermal titration calorimetry; RU, repeat unit.

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Introduction

Carbohydrate—protein interactions are ubiquitous in nature and mediate the exchange of specific information (Gabius et al., 2011). The affinity of proteins towards sugars is tightly linked to the functional context of the respective interaction. It is therefore very important to study the driving forces for these recognition events and to understand in which way structural features of protein—carbohydrate complexes influence the thermodynamics and the mechanism of binding. Whereas energetics of protein—protein-interactions and protein folding have been studied in detail (Baldwin, 2007) and linked to structure, insight into thermodynamics of protein—carbohydrate interactions is far more incomplete. One important reason for this is the obvious lack of high resolution crystal structures of proteins in complex with oligosaccharides of more than two monosaccharide building blocks. Analysis of non-covalent protein—carbohydrate complexes in the Protein Data Bank showed that about 80% of the ligands were monosaccharides, 13% were disaccharides, and 4% tri- to pentasaccharides (Nakahara et al., 2008). The remaining 3% were mainly hexa-, hepta- or octasaccharides; however their majority mediates protein contacts only via small interfaces of one or two monosaccharide building blocks. This is in accordance with the fact that fundamental research about protein—carbohydrate complexes has mainly focused on lectins, proteins that particularly bind small saccharide units. Thermodynamics of complexes between carbohydrates and lectins have been intensively studied (Ambrosi et al., 2005; Dam and Brewer, 2002; Toone, 1994; Weis and Drickamer, 1996). A variety of methods has been used, like equilibrium dialysis, fluorescence spectroscopy, NMR, capillary electrophoresis or surface plasmon resonance (Lee and Lee, 2003). Global thermodynamic data analysis is achieved in isothermal titration calorimetry (ITC), where parameters like affinity, enthalpic and entropic contributions to the free enthalpy of binding as well as changes in heat capacity (ΔCp) can be obtained in a single experiment, or in experiments at different temperatures, respectively (Christensen and Toone, 2003). Lectins have weak affinities for monovalent sugars and broad specificities for oligosaccharides. Typical dissociation constants are in the millimolar range for monosaccharides and in the micromolar range for oligosaccharides (Ambrosi et al., 2005; Weis and Drickamer, 1996). Binding sites in lectins are largely preorganised shallow grooves and no major structural rearrangement of the proteins is observed upon complex formation. By contrast, in antibodies deeper binding pockets are found with high binding affinities that have been attributed to the hydrophobic effect. Therefore, small but significant negative ΔCp values (less than $0.5\,\text{kJ}\,\text{mol}^{-1}\,\text{K}^{-1}$) are observed upon lectin—carbohydrate complexation (Toone, 1994). Consequently enthalpy—entropy compensation is observed; however, with a flatter slope of the enthalpy—entropy plot than found for proteins (Garcia-Hernandez et al., 2003).

High-resolution structural information on the interaction of proteins with oligosaccharides of more than five building blocks is sparse. Although some lectins have been found to bind longer oligosaccharides with higher affinities than smaller sugar units, structural information on the complexes is often lacking. Extended polymeric carbohydrate structures, often present as components of plant cell walls or storage polysaccharides are substrates for bacterial glycoside hydrolases that contain independent domains termed carbohydrate binding modules (CBMs) to target and concentrate the enzymes on their substrates (Abbott and Boraston, 2012). Crystal structures and affinity studies of CBMs in complex with oligosaccharides revealed characteristic elongated shallow binding sites with few hydrogen bonds and mainly aromatic side chains mediating the contact. Consequently, the quantity of stacking interactions was well described by accumulation of ΔCp-values predicted for desolvation of tryptophan or tyrosine in proteins (Zolotnitsky et al., 2004). Tailspike proteins (TSP) from bacteriophages are well studied model systems for protein folding, but also have been investigated for their role during the bacteriophage's infection process (Andres et al., 2010a, 2010b, 2012). TSP

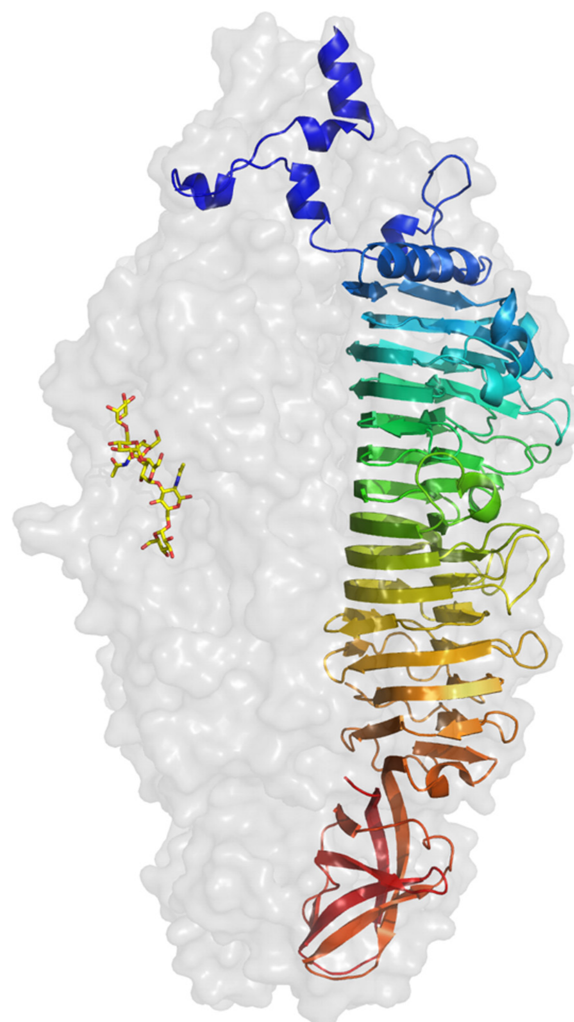

Figure 1 Structure of HK620TSP with oligosaccharide binding pocket. Structure of bacteriophage HK620 tailspike trimer lacking the N-terminal capsid binding domain. Side view of a surface representation with one subunit as a ribbon drawing gradually coloured from N-terminus (blue) to C-terminus (red). Each subunit has an O-antigen binding site; as an example an O-antigen hexasaccharide of *E. coli* serogroup O18A1 is shown in stick representation. Figure generated with PyMOL (SchroedingerLLC, 2015).

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