What contributes to an effective mannose recognition domain?

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Author(s) Sager, Christoph P.; Eriş, Deniz; Smieško, Martin; Hevey, Rachel; Ernst, Beat
Author(s) at UniBasel Ernst, Beat ; Sager, Christoph ; Hevey, Rachel ; Eris, Deniz ; Smiesko, Martin ;
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In general, carbohydrate-lectin interactions are characterized by high specificity but also low affinity. The main reason for the low affinities are desolvation costs, due to the numerous hydroxy groups present on the ligand, together with the typically polar surface of the binding sites. Nonetheless, nature has evolved strategies to overcome this hurdle, most prominently in relation to carbohydrate-lectin interactions of the innate immune system but also in bacterial adhesion, a process key for the bacterium's survival. In an effort to better understand the particular characteristics, which contribute to a successful carbohydrate recognition domain, the mannose-binding sites of six C-type lectins and of three bacterial adhesins were analyzed. One important finding is that the high enthalpic penalties caused by desolvation can only be compensated for by the number and quality of hydrogen bonds formed by each of the polar hydroxy groups engaged in the binding process. In addition, since mammalian mannose-binding sites are in general flat and solvent exposed, the half-lives of carbohydrate-lectin complexes are rather short since water molecules can easily access and displace the ligand from the binding site. In contrast, the bacterial lectin FimH benefits from a deep mannose-binding site, leading to a substantial improvement in the off-rate. Together with both a catch-bond mechanism (i.e., improvement of affinity under shear stress) and multivalency, two methods commonly utilized by pathogens, the affinity of the carbohydrate-FimH interaction can be further improved. Including those just described, the various approaches explored by nature to optimize selectivity and affinity of carbohydrate-lectin interactions offer interesting therapeutic perspectives for the development of carbohydrate-based drugs.
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