Selectivity of glycosaminoglycan recognition by proteins. Towards understanding the internalization of macromolecules by cell surface proteoglycans

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Glycosaminoglycans (GAGs) orchestrate several key biological functions by binding to cell surface proteins and their receptor complexes. Researchers have been trying to understand specificity of GAG binding to proteins. Unfortunately, identifying specificity elements is challenging because of large number of sulfation patterns and high sugar ring flexibility. An efficient approach is to screen all possible GAG sequences using computational tools. Recent exhaustive screening of a library of heparan sulfate hexasaccharides using our computational technology yielded a highly distinct sequence (IdoA-GlcNS-GlcA2S-GlcNS6S-GlcA2S-GlcNS) that selectively bound heparin cofactor II (HCII) but not antithrombin. To identify general GAG recognition elements, we utilized molecular dynamics simulations of eight unique heparan sulfate sequences that are 12 residues long. The 8 12-mers contained all NS domains, all NA domains and combination of NS-NA-NS domains. We selected the GAG binding alpha helix of HCII as the protein-binding partner. This sequence has the Cardin and Weintraub consensus sequence. MD simulations over a microsecond time scale showed that lack of sulfation, as in NA domain, induced significant plasticity in the interaction of HCII-helix with the 12-mer. For the NS domain, the interaction was found to be strong and induced un-folding of the helix. Interestingly, chains devoid of the N-sulfate group exhibited limited translational movement of HCII helix along the chain. On the other hand, chains with N-sulfate groups but devoid of 6-sulfate groups allowed translational movement as well as reorientation of the helix. For the NS-NA-NS domain containing 12-mer, translational motion of the HCII helix was once again restricted, especially because of the NA domain. Comparison of translational motion of several sequences along the GAG axis revealed that the GlcA2S residue is particularly capable of engineering higher level of specificity of interaction. This correlates with our earlier observations on the HS – HCII system. Finally, similar studies on the C-terminal helix of neutrophil activating chemokine CXCL1 shows absence of such restricted recognition indicating lack of selectivity. Overall, this work reveals for the first time how selectivity of GAG recognition contributes to translational movement of proteins, which is expected to be important for understanding endocytosis of certain macromolecules engineered by cell surface proteoglycans.