The role of charged surface residues in the binding ability of small hubs in protein-protein interaction networks

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Hubs are highly connected proteins in a protein-protein interaction network. Previous work has implicated disordered domains and high surface charge as the properties significant in the ability of hubs to bind multiple proteins. While conformational flexibility of disordered domains plays an important role in the binding ability of large hubs, high surface charge is the dominant property in small hubs. In this study, we further investigate the role of the high surface charge in the binding ability of small hubs in the absence of disordered domains. Using multipole expansion, we find that the charges are highly distributed over the hub surfaces. Residue enrichment studies show that the charged residues in hubs are more prevalent on the exposed surface, with the exception of Arg, which is predominantly found at the interface, as compared to non-hubs. This suggests that the charged residues act primarily from the exposed surface rather than the interface to affect the binding ability of small hubs. They do this through (i) enhanced intra-molecular electrostatic interactions to lower the desolvation penalty, (ii) indirect long – range intermolecular interactions with charged residues on the partner proteins for better complementarity and electrostatic steering, and (iii) increased solubility for enhanced diffusion-controlled rate of binding. Along with Arg, we also find a high prevalence of polar residues Tyr, Gln and His and the hydrophobic residue Met at the interfaces of hubs, all of which have the ability to form multiple types of interactions, indicating that the interfaces of hubs are optimized to participate in multiple interactions.

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