Adhesive water networks facilitate binding of protein interfaces

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Water structure plays an essential role in biological assembly. In the case of hydrophobic surfaces extensive studies have documented hydrophobic dewetting in protein folding [1,2] and binding [3]. In contrast, dewetting is unlikely to occur during assembly of hydrophilic interfaces, which are also of high relevance in protein:protein6 and protein:DNA interaction, and their mechanism of assembly remains mysterious. Due to its high dielectric constant water screens the direct electrostatic interactions between oppositely charged ions so that it is naturally considered as a very good solvent of small hydrophiles. On the supramolecular level, however, as evidenced by the binding of hydrophilic and charged interfaces, water obviously does not play this role. To understand the unusual behavior of water on this scale, we have studied here the assembly of two hydrophilic protein interfaces. Our extensive real time atomistic molecular dynamic simulations for protein-protein assembly reproducibly recovered the native bound state of the Barnase:Barstar complex and thus give atomistic insight into the mechanism of binding. The simulations showed that the structured water in the interfacial gap forms an adhesive hydrogen bond network between the interfaces. This network already plays an important role during the diffusive phase in reducing the dielectric shielding properties of the water and stabilizes early intermediate states before native contacts are formed. The transformation from these intermediates to the stereo-specific complex is then accompanied by maximization of the interfacial water-mediation. This work reveals new physical properties of liquid water as interfacial glue between hydrophilic interfaces.

[1] P. Liu, X. Huang, R. Zhou, B. Berne, *Nature*, **2005**, 437, 159-162.
[2] D. Chandler, *Nature*, **2005,** 437, 640-647.
[3] M. Ahmad, W. Gu, V. Helms, *Angew. Chem.-Int. Ed.,* **2008,** 47, 7626-7630.