Atomistic Simulations of a Peptide-Receptor Complex with Extremely Weak Binding Affinity

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We have used molecular dynamics (MD) simulations to study the extremely weak, but specific binding of the hNIFK heptapeptide with the FHA domain of human antigen Ki67 (Ki67FHA). This binding interaction has a dissociation constant (K_d) of 42 ± 5 mM and implicates a biological role for Ki67 in signaling pathways for cell proliferation[1]. As determined by NMR spectroscopy, the hNIFK heptapeptide is natively unfolded in its unbound state and extends the β-sheet of the Ki67FHA receptor upon binding. Specific hydrophobic contacts as well as hydrogen bonds form between the heptapeptide and the receptor upon binding. We will investigate the specificity of these contacts by performing simulations from two different binding orientations in which the β-sheet register is shifted by two hydrogen bonds. We will also test the opposite orientation of the peptide. Consistent with experimental conditions, we will perform the simulations at constant temperature (300 K) and pressure (1 atm) in boxes of explicit water molecules with an ionic strength of 150 mM NaCl. Future work will focus on determining the underlying thermodynamic basis for the formation of the weak, but specific binding of the hNIFK heptapeptide to the Ki67FHA receptor.

FHA domain-heptapeptide: At left is shown the FHA domain receptor-heptapeptide complex. The red β-strand is the heptapeptide portion of hNIFK that extends the β-sheet of FHA. The blue strands interact via hydrogen bonds and hydrophobic contacts with the heptapeptide.

(1) Byeon, In-Ja L, et al. "Sequential Phosphorylation and multisite interactions characterize specific target recognition by the FHA domain of Ki67". Nature Structural & Molecular Biology 12.11 (2005): 987-993.