Assessing the stability of a drug-like inhibitory peptide in complex with *β*-Catenin using umbrella sampling

F. Ghobadi, H. Mahdiuni*
Department of Biology, School of Sciences, Razi University, Kermanshah, 67149-67346, Iran
*hmahdiuni@razi.ac.ir

Abstract: Designing new peptides as potential drugs with the ability to interrupt protein-protein interactions has been an effective approach towards treatment of many diseases including cancers in the past decades. Pancreatic cancer has one of the lowest survival rates with above 40,000 deaths reported in the United States in 2015 [1]. Because of poor prognosis and high drug resistance observed in pancreatic cancer patients, designing novel drugs that can inhibit related pathways is critical. LRH-1/*β*-Catenin complex has an important role in Wnt signaling pathway which has been shown to be upregulated in this type of cancer [2]. Our aim in this study was to evaluate the interaction stability of an inhibitory peptide (with the sequence of DDMEMPQQTE) which was previously designed by peptidomimetic strategy, in complex with the protein *β*-Catenin. Since this peptide is structurally similar to the original ligand's interacting surface, we could achieve an assessment by comparing the free energies of the protein-peptide interaction to the original interaction between *β*-Catenin and LRH-1. For this purpose, we performed umbrella sampling, a computational technique, which uses steered molecular dynamics simulation to break down a non-ergodic system into several ergodic systems [3]. At the first step, we considered *β*-Catenin as the fixed reference group and the peptide as the mobile group, which was pulled away from *β*-Catenin along a reaction coordinate. The reaction coordinate is the line between our reacting groups' center of masses. Since we had to employ this center of mass pulling over a very short period of time and our system's dynamic behavior differs considerably during the reaction, we needed to break our trajectory into smaller pieces (simulation windows) at specific points with equal distances. At the end of this step, a number of configurations were produced as starting configurations for each simulation window, wherein separate MD simulations were carried out as the second step of the process. Finally, we attained a diagram indicating the reaction's PMF (Potential of Mean Force) as a function of distance. We performed this process for two specific peptides: one was the designed peptide with high affinity for *β*-Catenin and the other was the reference LRH-1 fragment used as the template for designing the inhibitory peptide. Analyzing and comparison of the results can lead us to an evaluation of the complex stability and the designed peptide efficacy in interrupting LRH-1/*β*-Catenin interaction.

Keywords: Umbrella Sampling, Inhibitory Peptide, LRH-1; *β*-Catenin

References

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