Ninnutt Moonrin 2014: Molecular Dynamics Simulations of Mitogen-Induced Gene-6 Segment 1 (MIG-6_s1) Peptide to the Activated Epidermal Growth Factor Receptor Kinase Domain Targeting the Asymmertric Dimer Interface. Master of Science (Biochemistry), Major Field: Biochemistry, Department of Biochemistry. Thesis Advisor: Assistant Professor Kiattawee Choowongkomon, Ph.D. 201 pages.

The over-expression of EGFR is associated with human cancers and drug resistant of the mutated EGFR is also a problem thus the C-lobe of EGFR kinase might be a new target for EGFR kinase activity inhibition. MIG-6 is a key in controlling the EGFR over-expression. In order to design a potency MIG-6_s1, the molecular dynamics (MD) simulations and binding free energy were applied to examine the basis protein-peptide interactions between EGFR kinase/MIG-6_s1 on interfaces. The molecular mechanics Poisson-Boltzmann and Generalized-Born surface area (MM-PB/GBSA) methods were performed to predict binding free energy. Van der Waals and non-polar solvation were the major favorable driving forces for binding process. The crucial residues on interface were obtained by free energy decomposition and several key residues were also proven the important for binding by computational alanine scanning approach. We had used the basis information from our study of EGFR kinase/MIG-6_s1 interactions to design short peptide of MIG-6_s1 together with *in silico* site-direct mutagenesis. MM-PBSA calculation was able to successfully rank the binding affinities of all four models in the following order: T349R/S351R> T349R> wild-type> S351R. The double mutant T349R/S351R bound EGFR kinase was predicted the highest binding affinity. The increasing of electrostatic potential in all mutations was revealed in free energy shift, which might be influenced by charge-charge interaction with the capability of guanidinium side-chain of arginine to salt-bridge formations. To prove the electrostatic effect by charge-charge interaction, not only salt-bridge analysis could confirm this phenomenon through hydrogen bond interaction but the free energy components of the mutated residues were also analyzed. They were made sure that arginine substitutions could increase not only the electrostatic contribution but the capability of their side-chains could also increase van der Waals interaction. The synergistic effect was explained the effect of two mutated sites in double mutation in term of the coupling free energy. These results permitted the mutations of positions 349 and 351 in an optimized sequence of MIG-6_s1 to significantly enhance binding affinity. These approaches revealed in this study might be helpful in the design of new EGFR kinase inhibitors toward the C-teminal lobe of EGFR kinase interface.

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