A Precision Medicine Approach: In silico Analysis of a Novel Anti-Tumor Peptide as a Future Targeted Therapy

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The phosphoinositide 3 kinase pathway (PI3K) may be among the most important pathways regarding the onset of mammalian cancer, as it modulates a multitude of cell regulatory processes, making inhibition of this specific pathway an appealing target for cancer treatments. More recent research suggests that targeting isoform specific subunits of Class I PI3K, specifically the catalytic PIK3CB/p110 beta subunit would yield an effective, yet precise drug to limit activation of this pathway. This study utilized computer modeling to examine and identify the mechanism of an 18 residue PIK3CB/p110 beta specific motif (Selectide-18) and its truncated models on a molecular level. Predictive peptide models were generated for all continual sequences of Selectide-18 from 6 to 18 residues using PEP-FOLD 3.5. The five most likely models for each mutant were chosen to proceed with docking simulations on the PI3K regulatory subunit, p85 alpha using AutoDock Vina. Each simulation predicts thousands of potential docking positions and provides the 9 most plausible complexes along with their respective binding affinities. The binding positions and their proximity to the active sites of p85 alpha were examined using UCSF Chimera’s distance function. Moreover, the binding affinity and position of each truncated model was examined in comparison to Selectide-18. Several mutants, namely a nine amino acid fragment, yielded comparable docking affinities while simultaneously yielding better binding proximities than the wild-type. These truncated models are predicted to maintain the wild-type’s inhibitory potency while also yielding a drug with improved cellular permeability and decreased side effects.