Designing and screening of a biomimetic peptide library to select blocking peptides interupting β-catenin/LRH-1 complex in pancreatic cancerous cells

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Abstract: Pancreas cancer characterizes with late prognosis and weak treatment options. Intrinsic resistance to chemotherapeutic agents is the critical problem in pancreas cancer [1, 2]. In the lots of recent studies, LRH-1 transcription factor attends as one of the most important targets in pancreas cancer therapeutic options [3, 4]. LRH-1 employs β-catenin to upregulate *CCND1*, *CCNE1* and *C-MYC* genes in the Wnt signaling pathway. The result of that corporation and β-catenin/LRH-1 complex formation is the amplification and migration of the cancerous cells [5]. In the present research, we applied g-mmpbsa program implemented in GROMACS package for the initial β-catenin/LRH-1 complex atomic coordinate with PDBid: 3TX7 to obtain potential disruptive peptide(s). This program applied in 100ns MD simulation of the β-catenin/LRH-1 complex. It causes the presentation of the critical interface residues. After that, pairing total binding free energy calculations were done to reveal the affinity binding peptide motif as a decapeptide DXMXXPQQTE. In accordance to the constructed motif, a 6859-member library constructed in MATLAB programming and Modeller 9.17 software. After that, virtual screening processes organized by E_{hex} values, C-terminal position and RMSD analysis. The Rosetta flexpepdock server was applied to flexible docking of the peptide protein backbones. Consequently, the initial 6859-member search space decreased to 7 potential disruptive peptide candidates for the next experimental validation.

Keywords: β-catenin/LRH-1 complex; disruptive peptide; g_mmpbsa method; pancreas cancer; Hex docking.

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