Hightroughput structure-based virtual screening to repropose new inhibitory compounds against FoxM1 transcription factor overexpressing in pancreatic cancerouse cell lines

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Abstract: Pancreatic cancer is the fourth leading cause of cancer death worldwide. FoxM1 is an oncogenic transcription factor belonging to the Forkhead superfamily transcription factors which control cell cycle progression, differentiation, migration, invasion, angiogenesis, apoptosis and DNA damage repair. The overexpression of the FoxM1 is found in many types of the human malignansis such as pancreas, lung, liver, colon, cervix, and breast. Inhibition of the transcriptional activity of FoxM1 is important for decrease the rate of cancer progression and improves therapeutic options [1-3]. To reach that, in the current research, the starting atomic coordinates of the complex (PDB ID 3G73) was downloaded from Protein Data Bank and a precise 100-ns molecular dynamics simulation *in aquo* was performed for the cleaned FoxM1 coordinates to remove spatial clashes and prepare conformations for the next binding site prediction. The candidated binding sites of FoxM1 were predicted utilizing MDpocket algorithm [4] and eFindsite web server. After that, a library of the 4038 drug compound was downloaded from ZINC database. The ligands and the protein were ready for Vina docking [5] processe by removing the water molecules and adding polar hydrogens in the obabel program and using the pdbqt-maker shell script. Screening processes were done by the E-vina values and the visual inspection. At last, our analysis decreased the volume of the library from 4038 member to the 2 final compound which is subjected to the next experimental validations.

Keywords: FoxM1; pancrease cancer; Vina docking; MDpocket; eFindsite; ZINC database.

References

[1] Jaiswal, N., Chakraborty, S., & Nag, A. (2014). Biology of foxm1 and its emerging role in cancer therapy. *J Proteins Proteomics*, (5) 1-24.

[2] Koo, C. Y., Muir, K. W., & Lam, E. W. F. (2012). FOXM1: From cancer initiation to progression and treatment. *Biochim Biophys Acta*, (1) 28-37.

[3] Bella, L., Zona, S., Nestal de Moraes, G., & Lam, E. W. F. (2014). FOXM1: A key oncofoetal transcription factor in health and disease. *Semin Cancer Biol*, (29) 32-39.

[4] Schmidtke, P., Bidon-chanal, A., Luque, F. J., & Barril, X. (2011). MDpocket: Open-source cavity detection and characterization on molecular dynamics trajectories. Bioinformatics, (23), 3276–3285.

[5] Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, *J Comput Chem*, (31) 455-461.