Identification of potent VEGFR-2 Inhibitors of Angiogenesis through homology modeling, structure based virtual screening, docking and molecular dynamics simulations

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Abstract— VEGFR-2 is a known protein target for antiangiogenic agents, was used in this study. In order to understand of the mechanisms of ligand binding and the interaction between the ligand and the VEGFR-2. A three-dimensional (3D) model of the VEGFR-2 is generated based on the crystal structure of the complex containing KIT and sunitinib (PDB code 3G0E) by using the Modulle r9v11 software. With the aid of the MD simulation methods, the final refined model is obtained and is further assessed by SAVES server, which shows that the refined model is reliable. With this model, a flexible docking with screened compounds from Zinc database was performed by AutoDock in PyRx Virtual Screening tool. Ten lead molecules having better binding energy than query (Pazopanib). The binding interactions of compounds with active site of VP-3 model suggested that the amino acid residues (Glu13, Glu15, Leu57, Glu134, Cys136, Lys137, Gly215, Arg218, Asp 223, Arg247 and Tyr249) play a key role for drug design. The MD simulations were performed for VEGFR-2-Zinc14945139 (lead1) docking complex in NAMD v2.9. The Trajectory analysis showed docking complex and inter molecular interactions was stable throughout the entire production part of MD simulations. The predicted pharmalogical properties of best compounds, among them Zinc14945139 is well within the range of a drug molecule with good ADME profile. Hence, would be intriguing towards development of potent inhibitor molecule against VEGFR-2.

Index Terms— VEGFR-2, MD simulations, Molecular docking, Homology modeling, Zinc database, NAMD, VMD.

1 INTRODUCTION

Cadmium (Cd) is classified as a Type I human carcinogen and its causes angiogenesis. It is the process of growing new blood vessels from the preexisting ones [1]. It is not only important for normal physiological functioning but also critical for many pathological processes such as tumor initiation, proliferation, and metastasis [2, 3, 4]. It has been well established that angiogenesis is a fundamental requirement for tumor development. Studies have demonstrated that vascular endothelium could be a primary target of Cd toxicity [1, 4]. Some studies reported disruptive effects of Cd on human endothelial cells [5, 6]. The effect of Cd on reactive oxygen species (ROS), mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK), AKT, and p70S6K1 signaling pathways and the downstream proangiogenic factors hypoxia-inducible factor-1 (HIF-1) and VEGF in human lung epithelial cells. VEGF exerts its biological actions by binding to its two receptor tyrosine kinases expressed on endothelial cells, namely, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). VEGFR-1 is poorly autophosphorylated in response to VEGF in endothelial cells and is weakly involved in transducing the VEGF angiogenic signals. The evidences support the concept that VEGFR-1 might act as a decoy receptor rather than as a signal transducing molecule [7, 8], whereas ligand-induced homodimerization of VEGFR-2 leads to a strong autophosphorylation of several [9] tyrosine residues of VEGFR-2. It is essential for the morphogenesis of vascular endothelium and is the primary receptor mediating the angiogenic activity of VEGF through distinct signal transduction pathways that regulate endothelial cell proliferation, migration, differentiation and tube formation [10, 11]. The VEGFR-2 signaling pathway is a promising target of angiogenesis, because it is a common pathway for tumor-induced angiogenesis [12]. VEGF is viewed as an attractive therapeutic target for the development of novel anticancer agents [41]. There are several angiogenesis inhibitors in phase I or phase II clinical trials, including antibodies aimed at VEGF or VEGFRs [13, 14], soluble decoy receptors that sequester ligands [40] and small molecule inhibitors that inhibit [15] kinase activity. To exploit more efficient and safer agents for the treatment of angiogenesis-related diseases such as cancer, a large number of scholars have been actively pursuing small molecule therapeutic strategies targeted at VEGFR-2-mediated [16, 17] signal transduction pathway. In this study we use Pazopanib natural drug as a query screening compounds from drug databases. Pazopanib, which is being developed by GlaxoSmithKline plc, is an oral, second-generation multi-targeted tyrosine kinase inhibitor that targets VEGFR, platelet-derived growth factor receptor and c-kit, key proteins responsible for tumor growth and survival. Pazopanib exhibited good potency against all of the human VEGFRs and closely related tyrosine receptor kinases in vitro, and demonstrated antitumor activity in several human tumor xenografts, including renal cell carcinoma (RCC), and breast and lung cancer. In phase I and II clinical trials, Pazopanib was generally well tolerated with the main side effects being hypertension, fatigue or gastrointestinal disorders. Pazopanib alone caused a decrease in tumor size and stable disease in a significant number of patients, including those with RCC, NSCLC and gynecological tumors [18]. Finally, a virtual screening experiment was carried out to validate the effectiveness of the model and its ability to retrieve actives