Plausible Involvement of K634 and T681 mutations in modulation of tertiary structure of human PDGFR-β protein kinase domain by computational molecular dynamics analysis

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Abstract:

Platelet derived growth factor receptor beta (PDGFR-β) is expressed by endothelial cells (ECs) of tumor-associated blood vessels and regulates primarily in early hematopoiesis. Human PDGFR-β is a novel therapeutic target for glioblastoma (GBM). However, a major challenge of GBM therapy is to overcome drug resistance, mostly initiated by the missense mutations in the protein kinase catalytic domain. These mutations in PDGFR-β tyrosine kinase gene are associated with the development of various diseases such as cancers, infantile myofibromatosis, atherosclerosis and nephritis. The present work is aimed to carry the in silico structural studies on PDGFR-β wild-type (WT) and mutant type (MT) to reveal the probable mechanism of resistance related to anti-angiogenic and anticancer drug sunitinib. Due to lack of crystal structure the 3D structure of PDGFR-β kinase domain (WT) and (MT) was predicted and the docking analysis with sunitinib was carried. The molecular dynamic simulations of PDGFR-β (WT) and (MT) were commenced to disclose the differential structural alterations in the PDGFR-β kinase structure, dynamics, and stability. Our result shows that the overall affect of mutations in the residues K634A, T681M, T681F, T681I, and T681A led to destabilize the 3D structure of PDGFR-β and altered the binding energy of sunitinib. Specifically, the mutation at residue lysine 634 (K634A) and gatekeeper residue threonine 681 (T681M), present in the ATP binding pocket, affected the protein stability most, thus conferring the resistance to the drug sunitinib. Present findings markedly displayed the molecular interactions of sunitinib with 3D structure of PDGFR-β kinase structure (WT and MT) demonstrating differential binding of the sunitinib in (MT) PDGFR-β leading to developed resistance to chemotherapy. This is the first time that we have reported the comparison of drug resistance in PDGFR-β (MT) and (WT) structure using in silico methodology.