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Computational Investigation of V599 Mutations of BRAF Protein and Its Control over the Therapeutic Outcome under the Malignant Condition

Authors : Mayank, Navneet Kaur, Narinder Singh

Abstract : The V599 mutations in the BRAF protein are extremely oncogenic, responsible for countless of malignant conditions. Along with wild type, V599E, V599D, and V599R are the important mutated variants of the BRAF proteins. The BRAF inhibitory anticancer agents are continuously developing, and sorafenib is a BRAF inhibitor that is under clinical use. The crystal structure of sorafenib bounded to wild type, and V599 is known, showing a similar interaction pattern in both the case. The mutated 599th residue, in both the case, is also found not interacting directly with the co-crystallized sorafenib molecule. However, the IC50 value of sorafenib was found extremely different in both the case, i.e., 22 nmol/L for wild and 38 nmol/L for V599E protein. Molecular docking study and MMGBSA binding energy results also revealed a significant difference in the binding pattern of sorafenib in both the case. Therefore, to explore the role of distinctively situated 599th residue, we have further conducted comprehensive computational studies. The molecular dynamics simulation, residue interaction network (RIN) analysis, and residue correlation study results revealed the importance of the 599th residue on the therapeutic outcome and overall dynamic of the BRAF protein. Therefore, although the position of 599th residue is very much distinctive from the ligand-binding cavity of BRAF, still it has exceptional control over the overall functional outcome of the protein. The insight obtained here may seem extremely important and guide us while designing ideal BRAF inhibitory anticancer molecules.

Keywords : BRAF, oncogenic, sorafenib, computational studies
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