LIFETIME ANALYSIS OF TIME EVOLUTION OF INTERACTION OF SMALL-MOLECULE INHIBITORS OF PD-1 –PD-L1 AXIS WITH PD-L1 DIMER.

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The programmed cell death protein 1 (PD-1) and its ligand, PD-L1, constitute an important co-inhibitory immune checkpoint leading to downregulation of immune system. Tumor cells developed a strategy to trigger PD-1/PD-L1 pathway reducing the T cell anticancer activity. A number of antibodies targeting the PD-1/PD-L1 immune checkpoint pathway have been approved after successful clinical trials. Anti-PD-L1 small drugs, generally with improved pharmacokinetic and technological profiles than monoclonal antibodies, became an attractive research topic. At present, more than twenty small-molecular inhibitors (SMIs) of the PD-1/PD-L1 interactions whose scaffold is based on substituted biphenyl group connected to a further aromatic ring through a benzyl ether bond have been identified which act by inducing dimerization of PD-L1. Recently, based on the pharmacophore model, we have carried out the computational design of ten new small-molecular inhibitors (SMIs) of the PD-1/PD-L1 interactions, possessing a high-affinity binding towards the PD-L1 dimer. However, the full physical understanding of high-affinity binding of these compounds to the PD-L1 dimer is absent. Here, we use all-atom molecular dynamics simulations of four inhibitors of PD-1/PD-L1 interactions, BMS-1016, BMS-2007, BMS-4121, BMS-40210 together with PyContact software [2] to analyze time evolution of noncovalent interactions of key PD-L1-dimer residues with SMIs. Molecular dynamics simulations were performed using the GROMACS software with the CHARMM36 all-atom force field. The analysis has shown common for all four ligands the maintenance of key interactions with Tyr56A/B, Met115A/B, Ala 121B, Tyr123A/B during full simulation runs. In several cases stable hydrogen bonds with Gln66B, Ala121B and Asp122B took place. The results obtained suggest that hydrophobic protein-ligand interactions are the main cause of high binding affinity between considered BMS-ligands and the PD-L1 dimer resulting in high inhibiting activity of these ligands against PD-1/PD-L1 interaction.

Bibliographic references

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