IN-SILICO ANALYSIS OF PD-L1 DYNAMICS INDUCED BY SMALL-MOLECULAR INHIBITORS OF PD-1 –PD-L1 AXIS

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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. However, physical mechanisms of such dimerization remain unclear. Here, computational structural biology tools combining protein-protein and protein-ligand docking with molecular dynamics simulations were used to gain structural insights into the dynamics of PD-L1 induced by BMS-1165 recently shown to be one of the most potent small-molecular inhibitor of the PD-1/PD-L1 axis. The modeling of PD-L1-PD-L1 interaction was performed in a stepwise fashion using a four - staged computational molecular docking protocol (PIPER+GRAMM-X+HDOCK) – ROSETTADOCK – GalaxyRefineComplex – ROSETTADOCK (abbreviated by (P+G+H)RG_{RC}R). The PD-L1-BMS-1165 interaction was analysed using protein-ligand docking by the Glide protein-ligand software followed by molecular dynamics simulations. Molecular dynamics simulations were performed using the GROMACS software with the CHARMM36 all-atom force field. The modeling has shown that PD-L1 in the membrane environment exists as a dimer jointed by the PD-L1 N-terminal parts. The binding of the ligand to one of the monomers results first in the binding of another PD-L1 dimer to the ligand bound to the first dimer, followed by the dissociation of two monomers from both dimers and the formation of a trimeric complex including two PD-L1 monomers and the ligand between them

References

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