IN-SILICO ANALYSIS OF RESVERATROL-INDUCED PD-L1 DIMERIZATION

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T-cell activation through the blockade of PD-1/PD-L1 interactions is recognized at present as one of the most promising strategies in the cancer treatment and a number of antibodies targeting the PD-1/PD-L1 immune checkpoint pathway have been approved after successful clinical trials. However, the use of antibodies suffers from a number of shortcomings including poor tissue and tumor penetration, long half-life time, poor oral bioavailability, and expensive production costs. Small-molecule-based therapeutic approaches offer the potential to address the shortcomings of the antibody-based checkpoint inhibitors. 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. Very recently, the dietary polyphenol resveratrol (RSV) has been reported to inhibit the PD-1/PD- L1 interactions through the induction of the PD-L1 dimerization but the mechanisms 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 mechanisms of the RSV-induced dimerization of PD-L1. 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). Protein-ligand interactions were analysed using protein-ligand docking with Glide 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 a rather high intermolecular shape and polar complementarity in the PD-L1-PD-L1- RSV complex thus explaining the induction of PD-L1 dimerization and inhibition of PD-1-PD-L1interaction.

References

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