Molecular Docking of Peptides and Small Molecules into TRAF Proteins

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We present molecular docking studies of small and peptidic ligands binding to the TRAF6 and TRAF2 proteins. When a member of the tumor necrosis factor receptor (TNFR) family associates with a tumor necrosis factor (TNF) ligand, TNFR-associated factors (TRAFs) are the first molecules to bind to the activated TNFR. TRAF6 is the only TRAF family member that is known to participate in signal transduction of both the TNFR family and the interleukin-1/Toll-like receptor family. It is important for lymph node organogenesis and for the development and maturation of dendritic cells, mammary glands, skin, and the central nervous system. As TRAF6 plays a major role in the immune response to severe bacterial infection, it was proposed as a suitable target in septic shock with multiple organ failure. We performed molecular docking experiments of TNFR family peptides into TRAF6 protein using DynaDock [1]. Re- and cross-docking experiments of TRAF6 protein-peptide crystal complexes showed that this algorithm is capable of predicting docked conformations of high accuracy. Thus, DynaDock [1] was applied for TRAF6 protein-peptide docking of different TNFR peptide fragments which were experimentally identified as TRAF6 binding sequences. The peptides were modeled by means of the side chain prediction tool IRECS (Side-Chain Prediction by Iterative REduction of Conformational Space) [2].

TRAF2 protein is involved in B and T-cell signalling, inflammatory responses, organogenesis and cell survival. This protein interacts with a wide range of TNFRs like TNFR1, TNFR2, LMP1, CD40, and RANK. It is important for classical and alternative NF-κB activation pathways as well as for MAPK and JNK activation. TRAF2 plays a role as tumor suppressor in B-lymphocytes and therefore in the pathogenesis of chronic lymphatic leukemia. We investigated the binding modes of two peptide fragments of the LMP1 and CD40 proteins known to bind to TRAF2 by DynaDock [2] and studied the potential inhibition of the TRAF2 peptide binding site by small compounds using the docking tool AutoDock [3]. In accordance with ELISA-based assays, we could predict energetically favorable bound conformations for three compounds which specifically interfere with LMP1 binding to the TRAF2 protein.

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