In silico Design of a PD-1/TCR Bispecific T-Cell Engager for Targeted Immunotherapy in T-Cell Malignancies

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T-cell malignancies are aggressive hematologic cancers with limited targeted treatment options and high relapse rates. These malignancies are characterized by the overexpression of the PD-1 receptor, which promotes cancer cell survival and immune evasion, making it a promising therapeutic target. Immunotherapy using targeted T cells with reduced side effects is gaining popularity in cancer studies. This study aims to design a Bispecific T-cell engager that simultaneously binds the PD-1 receptor on malignant T cells and the TCR on T lymphocytes, thereby redirecting cytotoxic activity toward tumor cells. Protein sequences for TCR a (UniProt ID: P01848), TCR ß (UniProt ID: P01850), and PD-1 were retrieved from UniProt and modeled using AlphaFold to predict their 3D structures. Humanized single-chain variable fragment (scFv) structures for BiTE design were obtained from the SAbDab database. Molecular docking simulations were performed using the HDOCK server to assess the binding interactions between the engineered BiTE components and their respective targets. Further analysis identified strong binding energies for scFv (PDB ID = 9MIC for the PD1 receptor and 9CPH for the TCR receptor) and revealed stable hydrogen bonds and hydrophobic interactions at the predicted epitope sites. In future studies, I will perform chemical mutations to further strengthen the binding interactions. These findings demonstrate the potential of PD-1/TCR-targeted Bispecific T-Cell Engager as a novel immunotherapeutic strategy for T-cell malignancies, warranting further optimization and in vitro validation.

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