BIO.13 - Computational insights into the molecular interactions of anti -PD1/anti-DLL1 dual antibodies

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Introduction: Cancer is the name used to characterize a heterogeneous group of disorders marked by cells that do not respond to normal controls of division. Conventional therapies to treat such disorders, such as chemotherapy, are not targeted and have deleterious effects on healthy cells. Immunotherapy emerges as an alternative, having the potential to be a more specific treatment, where T cells have been the focus in the therapeutic manipulation of the endogenous antitumor immunity. Its activation is dependent on a balance between stimulatory and costimulatory signals, called immunological checkpoints. Pidilizumab is a bispecific monoclonal antibody (mAb) that binds to the PD-1 checkpoint receptor, enhancing the endogenous antitumor activity, and to the Notch ligand DLL1, thus inducing the transcription of genes directly correlated with Notch1 in lymphocytes, and could function as a tumor suppressor. Very little is yet known about how the interactions between such proteins are established.

Objective: Obtain the structure of scFv-like ("single-chain variable fragment") antibody fragments from the Pidilizumab mAb, and analyze the binding modes of these models with their PD1 and DLL1 ligands.

Methodology: To obtain the scFv structure, computational modeling of the light and heavy chains was performed with Modeller v. 9.20, using as template the three-dimensional structures of proteins that are deposited in the Brookhaven Protein Data Bank (PDB) which obtained greater similarity to the sequence submitted for analysis by BLAST. The models generated were evaluated according to the DOPE score and to the Modeller objective function. Three flexible ligand peptides of 10, 12 and 15 aminoacid residues, respectively, were added to connect the light and heavy chains. These models were submitted to Procheck and Molprobity in order to validate and to Coot to refine the structure.
For the analysis of the binding modes, the structures for DLL1 and PD1 were obtained from the PDB and used in the molecular docking, performed with the SnugDock program, from the RosettaAntibody package. The structures were grouped according to their RMSD and evaluated from the score generated by the program. The complexes were submitted to the PDBePISA server in order to find polar interactions at the interface between the proteins.

Results: Three-dimensional models for the variable fragments of the light and heavy chains were obtained. The addition of the three linkers resulted in a total of three different models, which after being refined were used in the molecular docking with PD1 and DLL1. Therefore, six complexes were obtained and the interactions between the proteins were analyzed.

Conclusion: It was possible, through the use of computational tools, to obtain 3 scFv models based on Pidilizumab, as well as obtaining the complexes between them and their two antigens, giving a better understanding of how the interactions that allow the complexes formation are established.

Keywords: Immunotherapy; Cancer; Pidilizumab