BIO_11 - Computational design of neutralizing scfv for gastric cancer protein CLDN6

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Introduction: Gastric cancer (CG) is one of the five major malignant tumors that seriously endanger human health. The expression of Claudin 6 (CLDN6) mRNA and protein is upregulated in CG cell lines and tissues, which indicated poor prognosis. Some genetic mutations can modify the expression of proteins and increase proliferation or decrease apoptosis, resulting in cancer. This is observed in CLDN6 associated with CG. Additionally, a promising therapy for cancer treatment is the use of single-chain variable antibodies (scFv), which retain the antigen-binding capacity and can be modified *in silico* to increase affinity and specificity. Computational biology has been used in the detailed study of protein structures and screening of new drugs. We used comparative modeling and protein-protein docking, in association with site-directed mutagenesis to optimize the structure of scFvs.

Objective: Thus, the objective of this work is to develop, by computational methods, specific scFvs able to dock and possibly neutralize the CLDN6 protein.

Methodology: So, the structure of pembrolizumab, used as scaffold, was obtained from the Protein Data Bank (PDB), along with the CLDN6, whose structure is not yet deposited in the PDB and was modeled with MODELLER using the amino acid sequence obtained from Uniprot. The scFv linkers ranged among 5 different lengths: GGGGS; GGGGSGGG; (GGGGS)2; [(GGGGS)2GGG] and (GGGGS)3 and were modeled with the ModLoop server. The HDOCK server performed Protein-scFv Docking, and the best complexes were selected using the PD1-Pembrolizumab control structure.

Results: On those grounds, the linker of scFvs and CLDN6 were modeled. After docking, we selected 3 complexes: scfv- CLDN6 with scFv of GGGGS, (GGGGS)2, and (GGGGS)3, which showed calculated binding affinities of -12.3 kcal/mol, - 12.4 kcal/mol, and -11.7 kcal/mol, respectively. In addition, they showed interaction with residues from the variable heavy chain of scFvs: GGGGS with residues ASN59, ARG102, and TYR35; (GGGGS)2 with residues ASN59, ARG99, and ARG102; and (GGGGS)3 with residues ASN59, ARG99, ARG102, TYR35.

Conclusion: In conclusion, the cited complexes can provide information for the design of specific antibodies for CLDN6, so the mutagenesis will be performed to optimize the scFv for the target.

Keywords: Cancer Gastric; scFv; CLDN6