Designing Of Peptide Based Multi-Epitope Vaccine Construct Against Gallbladder Cancer Using Immunoinformatics And Computational Approaches

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Abstract

Gallbladder cancer (GBC) is an aggressive and difficult to treat biliary tract carcinoma characterised by late presentation, poor prognosis, and a survival rate of <1 year. GBC is difficult to treat and the current treatments have yielded dismal outcomes. The aim of this study was to design a multi-epitope vaccine candidate against GBC using immunoinformatics approaches.

Three proteins including 5ʹ-Nucleotidase isoform 2 (NT5E), Aminopeptidase N (ANPEP) and Membrane metallo-endopeptidase (MME) are reported to be over expressed in different stages of GBC and are implicated in suppression of T cells and promoting cancer progression. Stimulation of immune system is critical in combating cancer and peptide based epitope vaccines have demonstrated the capability of generating a cancer specific immune response. ImmunoInformatics approaches allows for identification of the potential immunogenic and antigenic T and B cell epitopes that trigger a desired immune response, CTL, HTL and B-cell epitopes from NT5E, ANPEP and MME were predicted and screened on the basis of immunogenicity, antigenicity, allergenicity, toxicity and IFN-γ inducing properties. The selected epitopes were connected using linkers and suitable adjuvant for designing final vaccine construct. The physicochemical properties were analysed followed by 2D and 3D structure generation, refinement and validation. The secondary and tertiary models of the vaccine were successfully generated and satisfactorily validated. Ramachandran plot of the final 3D model showed more than 90% of the residues in allowed regions and only 0.4% in disallowed regions. The binding affinity of vaccine construct with immune receptors (TLR 2, 3 and 4) was assessed through molecular docking and simulation. The average numbers of hydrogen bonds for vaccine-TLR 2, 3 and 4 complexes in simulation were 15.36, 16.45, and 11.98 respectively and remained consistent over a 100ns simulation period, which is critical for their function.

Representing both MHC I & II alleles, the maximum world population coverage was 93.78% for CTL epitopes and 81.81% for HTL epitopes, making it a promising candidate. The class I and class II epitopes showed excellent population coverage in prevalent geographic regions like India (74.02% & 74.99%), Japan (94.26% & 74.83%), Korea (91.97% & 85.32%), Chile (86.46% & 67.08%) among others.

The epitope vaccine demonstrated good solubility, stability and antigenicity with potential to elicit strong antibody and cell mediated immune responses through in-silco immune simulation. The results of this study provide a strong basis for further evaluation through in-vitro/in-vivo experimental validation of safety and efficacy of the designed construct.

Keywords: Immunoinformatics, Vaccine, Epitope, Antigenicity, Immunogenicity, TLR, GBC