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Lentiviral-Based Novel Bicistronic Therapeutic Vaccine against Chronic Hepatitis B Induces Robust Immune Response

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Abstract : Introduction: Over 360 million people are chronically infected with hepatitis B virus (HBV), of whom 1 million die each year from HBV-associated liver cirrhosis or hepatocellular carcinoma. Current treatment options for chronic hepatitis B depend on interferon-α (IFNα) or nucleos(t)ide analogs, which control virus replication but rarely eliminate the virus. Treatment with PEG-IFNα leads to a sustained antiviral response in only one third of patients. After withdrawal of the drugs, the rebound of viremia is observed in the majority of patients. Furthermore, the long-term treatment is subsequently associated with the appearance of drug resistant HBV strains that is often the cause of the therapy failure. Among the new therapeutic avenues being developed, therapeutic vaccine aimed at inducing immune responses similar to those found in resolvers is of growing interest. The high prevalence of chronic hepatitis B necessitates the design of better vaccination strategies capable of eliciting broad-spectrum of cell-mediated immunity(CMI) and humoral immune response that can control chronic hepatitis B. Induction of HBV-specific T cells and B cells by therapeutic vaccination may be an innovative strategy to overcome virus persistence. Lentiviral vectors developed and optimized by THERAVECTYS, due to their ability to transduce non-dividing cells, including dendritic cells, and induce CMI response, have demonstrated their effectiveness as vaccination tools. Method: To develop a HBV therapeutic vaccine that can induce a broad but specific immune response, we generated recombinant lentiviral vector carrying IRES(Internal Ribosome Entry Site)-containing bicistronic constructs which allow the coexpression of two vaccine products, namely HBV T- cell epitope vaccine and HBV virus like particle (VLP) vaccine. HBV T-cell epitope vaccine consists of immunodominant cluster of CD4 and CD8 epitopes with spacer in between them and epitopes are derived from HBV surface protein, HBV core, HBV X and polymerase. While HBV VLP vaccine is a HBV core protein based chimeric VLP with surface protein B-cell epitopes displayed. In order to evaluate the immunogenicity, mice were immunized with lentiviral constructs by intramuscular injection. The T cell and antibody immune responses of the two vaccine products were analyzed using IFN-γ ELISpot assay and ELISA respectively to quantify the adaptive response to HBV antigens. Results: Following a single administration in mice, lentiviral construct elicited robust antigen-specific IFN-γ responses to the encoded antigens. The HBV T- cell epitope vaccine demonstrated significantly higher T cell immunogenicity than HBV VLP vaccine. Importantly, we demonstrated by ELISA that antibodies are induced against both HBV surface protein and HBV core protein when mice injected with vaccine construct ($p < 0.05$). Conclusion: Our results highlight that THERAVECTYS lentiviral vectors may represent a powerful platform for immunization strategy against chronic hepatitis B. Our data suggests the likely importance of Lentiviral vector based novel bicistronic construct for further study, in combination with drugs or as standalone antigens, as a therapeutic lentiviral based HBV vaccines. THERAVECTYS bicistronic HBV vaccine will be further evaluated in animal efficacy studies.

Keywords : chronic hepatitis B, lentiviral vectors, therapeutic vaccine, virus-like particle
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