DEVELOPMENT AND CHARACTERIZATION OF A MURINE HEPATOMA MODEL EXPRESSING HEPATITIS C VIRUS (HCV) NON-STRUCTURAL ANTIGENS FOR EVALUATING HCV VACCINES

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Hepatitis C (HCV) is a highly prevalent blood-borne virus with infection of 2-3% of world population and high rate of chronicity (>70%) leading to chronic hepatitis, which often progress to cirrhosis and hepatocellular carcinoma. HCV- specific immune responses consisting of CD4 and CD8 T cells and virus neutralizing antibodies have been shown to eliminate HCV infections in humans and chimpanzees. Therefore, vaccines that can induce potent and durable anti-HCV T and B cell responses may have the potential to clear chronic HCV infections. A number of HCV vaccines have been tested clinically with limited success. One of the major limitations in developing effective HCV therapies is the lack of effective and reliable animal models due to the narrow host range of the HCV virus. The study described herein reports the generation of a murine hepatoma cell line expressing HCV non-structural proteins and its use in a metastatic tumor setting to test anti-tumor efficacy of bacterial and viral vector vaccines expressing the HCV non-structural genes. HCV-recombinant hepatoma cells formed large solid-mass tumors when implanted into syngeneic mice, allowing the testing of HCV vaccines for immunogenicity and anti-tumor efficacy. Using this model, we tested the therapeutic potential of recombinant anti-HCV-specific vaccines based on two fundamentally different attenuated pathogen vaccine systems - attenuated Salmonella and recombinant adenoviral vector based vaccine. Attenuated Salmonella secreting HCV antigens limited growth of the HCV-recombinant tumors when used in a therapeutic vaccination setting. The inhibition of tumor growth by Salmonella vector-based vaccines was significantly reduced in mice co-injected with an anti-CD8 antibody, suggesting a role by CD8+ cells in the vaccine efficacy. The model was also used to compare replication deficient and replication-competent but non-infectious adenoviral vectors expressing non-structural HCV antigens. Results showed overall greater survival and reduced weight loss with the replication-competent vector compared to the non-replicating vector. Our results demonstrate the novel recombinant murine hepatoma model expressing HCV non-structural antigens as a useful model for evaluating therapeutic vaccines against HCV. Vaccines that are capable of inducing potent anti-HCV immune responses that are capable of controlling aggressive and metastatic tumor growth in this model would likely have the potential to control chronic viral infections such as HCV. This novel approach is particularly interesting for the development of therapeutic vaccines.