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SYNBAD, A CLINICAL CANCER VACCINE CANDIDATE, INDUCES ANTIGEN-SPECIFIC T CELLS AND EXTENDS LIFE IN A THERAPEUTIC LIVER CANCER MODEL

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Background Hepatitis B virus (HBV) infection is associated with approximately 25% of liver cancer cases in the US and 56% worldwide. Low rates of HBV vaccination in people 50 years or older combined with the fact that HBV infection is highest amongst the 40–49 year old demographic (i.e. individuals born prior to 1986) is a cause for concern as the median age for liver cancer diagnosis is 66 years of age. Despite the impact of immunotherapies in liver cancer over the past decade, durable responses remain elusive. Our approach to significantly improving outcomes is to activate and mobilize tissue-resident and systemic cancer-specific T effector memory cells (T_{EM}), especially for the treatment of cancer in organs with low T cell count such as the liver.

Methods We synthesized a novel capsid-modified adenovirus, SynBAd, for use as a therapeutic cancer vaccine targeting systemic immunity without causing commonly-reported adenovirus-mediated hepatotoxicity. We further engineered SynBAd to express a polytope of HBV antigens to activate the elimination of HBV+ tumor cells. SynBAd, administered intravenously (IV) for systemic and liver-specific T cell activation, was evaluated in a tumor-protection mouse model of liver cancer.

Results IV administration of SynBAd expressing a polytope comprised of HBV epitopes significantly extended the lives of mice with a liver-localized tumor bearing the same epitopes in contrast to control animals. Moreover, recipients of SynBAd expressing an irrelevant antigen did not demonstrate comparable levels of protection. SynBAd further induced antigen specific CD8 T cell immunity in mice and a population of effector memory T cells at levels equivalent with those induced by human Adenovirus serotype 5 (Ad5). The virus predominantly localized to the liver and spleen and induced antigen-specific T cells though more robustly in the latter than Ad5. Although SynBAd is a potent immunogen, antibodies generated in mice immunized with Ad5 only weakly neutralized SynBAd infection in vitro, suggesting that preexisting Ad5 antibodies will not dramatically influence SynBAd efficacy.

Conclusions The model used is representative of colon metastases to the liver as well as HBV-driven hepatocellular carcinoma. Localization of the vaccine after administration, activation of antigen specific T cells, mobilization of effector memory T cells, and efficacy in the liver cancer model suggest that this platform promotes a systemic tumor controlling immune response with wide-ranging clinical potential beyond liver cancer.

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