

INTRATUMOR CHILDHOOD VACCINE-SPECIFIC CD4+ T CELL RECALL HELPS ANTITUMOR CD8 T CELLS

Michael Brown*, Zachary McKay, Yuanfan Yang, Darell Bigner, Smita Nair, Matthias Gromeier. *Duke University, Durham, United States*

Background PVSRIPO, a recombinant poliovirus derived from the live-attenuated Sabin oral polio vaccine strain, is being tested in multi-institutional phase II clinical trials for recurrent glioblastoma (NCT04479241) and unresectable, PD-1 refractory melanoma (NCT04577807) in combination with PD1 blockade. PVSRIPO capsid is identical to the Sabin vaccine strain and >99% identical to the inactivated Polio vaccine (IPOL, Salk), against which public health mandated childhood vaccination is near universal. In non-vaccinated mice, PVSRIPO mediates antitumor efficacy in a replication-dependent manner via engaging innate inflammation and antitumor T cells. Accordingly, it is anticipated that pre-existing immunity to PVSRIPO impedes antitumor therapy. However, recent evidence indicates that immunological 'recall', or reactivation of memory T cells, may mediate anti-tumor effects.

Methods The impact of prior polio vs control (KLH) vaccination on intratumor viral replication, tumor inflammation, and overall tumor growth after intratumor PVSRIPO therapy was assessed in murine tumor models. The role of polio capsid and tetanus recall antigens in mediating intratumor inflammation and antitumor efficacy was similarly studied in mice non-permissive to PVSRIPO infection. To mechanistically define antitumor effects of polio recall, B cell and CD8 T cell knock-out mice were used, in addition to adoptive transfer of CD4 + T cells from vaccinated mice. Intratumor polio or tetanus recall antigen therapy was performed after OT-I transfer (OVA-specific T cells) in the B16-OVA melanoma model to gauge antitumor T cell activity. Lastly, the inflammatory effects of polio and tetanus antigens was tested in human peripheral blood mononuclear cells (PBMCs).

Results Despite curtailing intratumor viral replication, prior polio vaccination in mice potentiated subsequent antitumor efficacy of PVSRIPO. Intratumor recall responses induced by polio and tetanus antigens also delayed tumor growth. Recall antigen therapy was associated with marked intratumor influx of eosinophils, conventional CD4+ T cells, and increased expression of IFN- γ , TNF, and Granzyme B in tumor infiltrating T cells. The antitumor efficacy of polio recall antigen was mediated by CD4+ T cells, partially depended upon CD8+ T cells, and was impaired by B cells. Both polio and tetanus recall antigen therapy bolstered the antitumor function of tumor-specific OT-I CD8+ T cells. Polio and tetanus antigens induced CXCL10 and type I/II/III IFNs in PBMCs in vitro.

Conclusions Childhood vaccine-specific CD4+ T cells hold cancer immunotherapy potential. In the context of PVSRIPO therapy, antitumor and inflammatory effects of polio vaccine-specific CD4+ T cell recall supersedes inhibitory effects of attenuated intratumor viral replication, and represents a novel mechanism of action.

Ethics Approval The animal work described in this study was approved by the Duke University IACUC.

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