HETEROLOGOUS PRIME BOOST VIRAL VECTOR VACCINATION PROVIDES PROTECTION AGAINST INTRACRANIAL SYNGENIC MURINE Glioblastoma

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Background Glioblastomas are immunologically ‘cold’ tumors with sparse cytotoxic T-cell infiltration. Therefore, viral vector vaccines may be a promising approach to boost the induction of glioblastoma-targeted T cells. It has been previously shown that heterologous prime-boost vaccination with chimpanzee-derived adenovirus ChAdOx1 and modified vaccinia Ankara (MVA) vectors can induce a high magnitude of CD8+ T cells specific for cancer-associated antigens and have therapeutic effects against mouse models of cancer. Therefore, we aimed to evaluate whether treating mice with ChAdOx1 and MVA vaccines targeting model tumor antigens and endogenous antigens could be beneficial in the prophylactic and therapeutic settings against syngeneic, intracranial murine glioblastoma.

Methods Murine glioblastoma cell lines were developed to express model tumour antigens. In addition, endogenous tumor-associated antigens and neoantigens were identified in murine glioblastoma lines using our novel Mouse nEoanTigen pRedictOr (METRO) antigen discovery pipeline. We then created ChAdOx1 and MVA vectors expressing model tumor antigens or endogenous antigen candidates, and we confirmed their immunogenicity via intracellular cytokine staining of ex vivo stimulated peripheral blood mononuclear cells or splenocytes. In the prophylactic tumor setting, mice were vaccinated with ChAdOx1 and MVA vectors expressing endogenous antigens or a model tumor antigen, then challenged with syngeneic intracranial wild-type or model antigen expressing tumors, respectively. In the therapeutic setting, mice bearing intracranial tumors were treated with vaccines in combination with checkpoint inhibitors after confirming tumor formation.

Results ChAdOx1 and MVA heterologous prime-boost vaccination generated a high magnitude of antigen-specific CD8+ T cells against a model tumor antigen. Furthermore, we confirmed the immunogenicity of some of the antigens identified by the METRO pipeline. Prophylactic vaccination targeting a model tumor antigen significantly increased the survival time of mice bearing intracranial tumors engineered to express the same antigen. Ongoing studies are investigating the efficacy of this vaccination strategy in the therapeutic setting.

Conclusions Our heterologous prime-boost strategy generates a high magnitude of antigen-specific CD8+ T cells that provide protection against the development of orthotopic glioblastoma tumors in mice. It remains to be seen whether these vaccines can provide a therapeutic benefit to mice bearing intracranial tumors, and the effects of vaccination on the remodeling of the tumor microenvironment and tumor-draining lymph nodes are yet to be determined. Preclinical data generated using our vaccine and tumor models may provide proof-of-concept to move these vaccines into clinical trials to treat patients with glioblastoma.

REFERENCE

Ethics Approval All animal work was approved by either the University of Oxford Animal Care and Ethical Review Committee and experimental procedures were carried out in accordance with the terms of the UK Animals (Scientific Procedures) Act Project Licenses P0D369534 and PB050649E; or by the National Cancer Institute-Bethesda Animal Care and Use Committee and experimental procedures were carried out in accordance with the terms of Protocol NOB-024.