Background Arginase-1 (ARG1) is involved in various processes that allow tumor cells to evade immune responses within the tumor microenvironment (TME). Numerous attempts to target ARG1 in clinical settings have been made thus far, though with limited success. Immunization against TME-related targets has emerged as a promising treatment approach. We previously demonstrated that vaccination against ARG1 enhances anti-tumor activity in murine models. This study aims to extend our earlier observations and clarify the underlying mechanism of the anti-tumor activity of the ARG1 vaccine.

Methods ARG1 expression was examined via multiplex immunofluorescence in a tumor microarray panel of different cancers and across various cell types. The anti-tumor activity of the ARG1 peptide vaccine was assessed in ARG1+ mouse models, MC38 and 4T1. We confirmed the vaccine-induced immune response using an IFN-gamma Elispot assay on splenocytes and tumor-isolated CD4 cells. Excised tumors were subjected to immunohistochemistry, RNA sequencing, qPCR, and flow cytometry analyses.

Results Tumor microarray analyses confirmed the expression of ARG1 within the TME across different cancer indications, identifying distinct populations of immune suppressive cells expressing this marker. ARG1 vaccine treatment in two ARG1+ tumor models, MC38 and 4T1, induced the expansion of ARG1-specific T cells and a reduction in tumor growth. This correlated with increased infiltration of CD4+ T cells in the TME and a reduction in ARG1 expression in the tumor-draining lymph nodes from 4T1-bearing mice. Furthermore, F4/80 cells isolated from MC38 tumors showed a diminished expression of ARG1, along with an increase in the expression of the FPR2 gene, which is associated with pro-inflammatory characteristics. The anti-tumor response of the ARG1 peptide treatment was further enhanced when combined with anti-PD-1 monoclonal antibodies or other vaccines. Additional analyses will explore the underlying cellular and molecular mechanisms of ARG1 vaccine treatment.

Conclusions ARG1 presents a compelling target within the TME for immunotherapy. Vaccination targeting ARG1 to promote T cell immunity leads to anti-tumor activity by shifting the balance from an immunosuppressive to a pro-inflammatory microenvironment. This presents an attractive alternative strategy to other existing approaches currently under nonclinical and clinical investigations. Our findings bolster the clinical development of an ARG1 vaccine as a potential therapeutic strategy for various solid tumors.

REFERENCE

Ethics Approval All animal experiments were conducted following national regulations and ethical guidelines. Experiment conducted in Denmark were reviewed and approved by the Danish Animal Experimentation Council and performed under license number 2022-15-0201-01209. Experiments conducted in the U.S. were approved by the Lankenau Institute for Medical Research (IACUC) and conform with AALAC guidelines.

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