Background Programmed Death Ligand 1 (PD-L1) is a type I transmembrane protein encoded by CD274 gene, its interaction with PD-1 inhibits T cell proliferation and activation to control immune response, and contributes to cancer progression and immune escape. The PD-1/PD-L1 blocking antibodies have shown clinical efficacy in many cancers, however drug resistance mechanisms in patients remain a key challenge. As an alternative and supplemental approach to PD-1/PD-L1 blockade, vaccination approach to promote T-cell immunity against PD-L1+ target cells has been proposed after the observation that effector/cytotoxic T cells reactive against PD-L1 are found in the peripheral blood of cancer patients and healthy individuals.1  2 Our current study aims to evaluate the efficacy and mechanism of PD-L1 peptide-vaccine using pre-clinical models.

Methods PD-L1 expression in mouse models was evaluated per IHC or IF. Mice were subcutaneously inoculated with tumor cells and treated with PD-L1 peptides formulated in Montanide adjuvant. Tumor growth was then monitored, organs and tumor samples were collected. Vaccine activity was determined per IFNγ Elispot assay. Tumor samples were processed for flow cytometry or molecular analysis; functional assays were performed on sorted tumor infiltrated lymphocytes.

Results PD-L1 expression was confirmed in MC38 and CT26 syngeneic murine models which were selected for tumor studies. PD-L1 peptide vaccination induced expansion of PD-L1 specific T cells identified by IFNγ recall responses in splenocytes from C57BL/6 or BALB/c mice, leading to reduced tumor growth in both MC38 and CT26 models, respectively. PD-L1 specific CD4+ and CD8+ T cells were detected in tumor infiltrating lymphocyte populations, suggesting that vaccine-induced T cells migrated to the tumor site. Furthermore, in vitro co-culture study showed that T cells from PD-L1 vaccinated animals effectively recognized and eliminated PD-L1+ cells. The anti-tumor effect observed in vitro was enhanced when combining PD-L1 treatment to other therapeutic approaches such as IDO1 peptide vaccine.

Conclusions Our data from preclinical murine models provide insights into the mechanism of peptide-based treatment against PD-L1. We highlight for the first time that PD-L1 vaccine-induced T cells localize to the tumor microenvironment where they target PD-L1 expressing cells thus reducing the immunosuppression at tumor site and leading to decreased tumor growth as observed in two different models. Combination of PD-L1 treatment with other immune-suppressive targets such as IDO1 also showed enhanced effect in vivo supporting further development of similar therapeutic strategies for the treatment solid tumors.

REFERENCES

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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