822 IL6R-BLOCKADE ABOLISHES THE ANTI-TUMOR EFFECT OF TGFβ-DERIVED IMMUNE MODULATORY VACCINATION IN A MURINE MODEL OF PANCREATIC CANCER

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Background The tumor microenvironment (TME) in pancreatic ductal adenocarcinoma (PDAC) is highly immunosuppressive and desmoplastic, which could explain the limited therapeutic effect of immunotherapy in this disease. We developed an immune modulatory vaccine with TGFβ-derived peptides that can target immunosuppression and fibrosis in a murine model of pancreatic cancer.[1] IL-6 has been shown to be a driver of PDAC pathogenesis and high levels of serum IL-6 is a negative prognostic marker in PDAC.[2] However, recent pre-clinical studies have shown that IL-6 is required for immunotherapy-driven regression of tumors.[3] The aim of this study was to assess the role of IL-6 in a context of active anti-tumor response induced by an immune modulatory vaccine with TGFβ-derived peptides in a murine model of pancreatic cancer.

Methods C57BL/6 mice were subcutaneously (s.c.) inoculated with Pan02 PDAC cells. Mice were treated s.c. at the base of the tail with MHC-I and II-restricted TGFβ1-derived peptides adjuvanted with Montanide ('TGFβ vaccine') and/or s.c. next to the tumor with anti-mouse IL-6R blocking antibody. The presence of treatment-induced TGFβ-specific T cells was assessed by ELISPOT. Changes in the immune infiltration in tumor samples were characterized by flow cytometry. IL-6 concentration was determined by ELISA. IL-6 expression in different cell subsets in the tumor was assessed by scRNAseq using a single-cell atlas of human PDAC from six publicly available datasets.

Results Treatment with TGFβ vaccine resulted in higher levels of IL-6 in tumor-conditioned media and higher expression of IL-6 in cancer-associated fibroblasts. scRNAseq analysis of human PDAC tumors confirmed that fibroblasts are one of the main sources of IL-6 in the pancreatic tumor. Blocking IL6R abolished the anti-tumor effect of TGFβ vaccine in a murine model of PDAC and impaired the immune response developed towards the MHC-II-restricted TGFβ1-derived peptide. Tumors from mice that received the combination treatment were less infiltrated by T cells than tumors from mice treated with TGFβ vaccine. IL6R blockade was associated with a higher infiltration of less differentiated and more suppressive macrophages.

Conclusions IL-6, which is mainly secreted by fibroblast in PDAC, is required for the anti-tumor efficacy of TGFβ vaccine in the Pan02 murine model of pancreatic cancer. Lack of IL-6 signaling impairs the development of vaccine-specific $CD4^+$ T cells and the infiltration of T cells in the tumor. In addition, it results in a higher presence of macrophages in the tumor and it polarizes their phenotype towards a less differentiated and more suppressive phenotype.

REFERENCES

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Ethics Approval Experimental procedures with mice were conducted according to Federation of European Laboratory Animal Science Association (FELASA) guidelines and under a license issued by the Danish Animal Experimentation Inspectorate (2021–15-0201–01001).

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