MODULATING TUMOR MICROENVIRONMENT WITH ARGINASE-1 SPECIFIC T CELLS

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Background IO112 is an immune modulatory cancer therapy under preclinical development to target arginase-1-expressing tumor cells and immune inhibitory myeloid cells, such as myeloid derived suppressor cells (MDSCs), and tumor associated macrophages (TAMs). Arginase-1 acts as a metabolic immune regulator at the tumor site by reducing availability of L-arginine to the infiltrating immune cells thus reducing T cell functionality and proliferation. Previously, we demonstrated that IO112 triggers activation of spontaneous CD4+ and CD8+ T-cell responses against arginase-1, found in both cancer patients and healthy individuals.¹ These T cells are present in the memory T cell compartment, and are activated in arginase-1 inducing conditions, such as presence of TH2 cytokines IL-4 or IL-13 in vitro.^{2 3} In this study we aimed to explore the role of arginase-1-specific T cells as immune modulators in immune homeostasis and tumor microenvironment for the development of IO112 immunomodulatory therapy.

Methods Human arginase-1-specific T cells were isolated and expanded for functional characterization of reactivity against arginase-1 expressing target cells as well as subsequent phenotyping of the targeted arginase-1 positive cells. Syngeneic C57BL/6 mouse tumor models were used to assess the therapeutic efficacy of IO112.

Results We show that arginase-1-specific memory T cells specifically recognize arginase-1 expressing cells, such as mRNA transfected autologous dendritic cells (DCs) and B cells as well as M2 polarized macrophages in vitro. In addition, activated arginase-1-specific T cells produce pro-inflammatory cytokines IFN γ and TNF α . Secretion of TH1 cytokines by these T cells suggests that they may act as potent immune modulators in the tumor microenvironment, since many arginase-1 expressing myeloid cells are not terminally differentiated and they can be re-polarized to an immunostimulatory, M1-like phenotype. We also observed that targeting of M2-polarized arginase-1 expressing monocytic leukemia cell line THP-1 with arginase-1-specific CD4+ T cells induces upregulation of PD-L1 on the THP-1 cells. Furthermore, we demonstrate anti-tumor activity of IO112 in syngeneic mouse tumor models (B16 and MC38), both as monotherapy and in combination with anti-PD-1 treatment. The therapeutic effect was associated with increased immune infiltration in the IO112-treated mice compared to the control.

Conclusions We demonstrate that arginase-1 specific T cells can influence the polarization of arginase-1-expressing immune cells. Our study provides evidence that IO112 immune therapy against arginase-1 is an attractive way of modulating the immune suppressive tumor microenvironment for therapeutic benefit. With this rationale, we are currently undertaking Investigational New Drug (IND) application enabling studies to explore this approach in a clinical setting.

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Ethics Approval This study was approved by the Scientific Ethics Committee for The Capital Region of Denmark and Danish Ethics Committee on experimental animal welfare.

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