IL-15 ENHANCES CYTOTOXICITY OF SIPULEUCEL-T FROM METASTATIC CASTRATION-RESISTANT PROSTATE CANCER PATIENTS BY ACTIVATING CD8+ T AND NK EFFECTOR CELLS

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Background: Prostate cancer is the most commonly diagnosed non-skin cancer in men, and metastatic castration-resistant prostate cancer (mCRPC) represents the most lethal form of the disease. Sipuleucel-T (sip-T) is an autologous active cellular immunotherapy approved by FDA for patients with mCRPC and has been shown effective in improving overall survival (OS) among individuals with mCRPC. To date, detailed analysis of the sip-T product has not been studied using an advanced mass cytometry approach. Here, we present high dimensional data describing the phenotype of sip-T in detail. Furthermore, we show the effects of IL-15 on the anti-tumor efficacy of sip-T using in vitro and in vivo studies.

Methods: We performed a comprehensive assessment of sip-T (n=13 samples) from 10 patients with mCRPC, using high-throughput mass cytometry (CyTOF) comprised of 37 different antibodies/markers. Furthermore, we performed CyTOF on control and IL-15 stimulated sip-T and identified changes in leukocyte subsets as well as markers of activation and exhaustion. Finally, we examined the effects of IL-15 on cytotoxicity of sip-T against human prostate cancer cells (LNCaP and DU145) using in vitro cytotoxicity assays and in vivo studies in NSG mice.

Results: CyTOF analysis revealed that CD3+ T-cells (including CD4+ and CD8+) constituted the highest proportion (median, range: 63%, 9-89%) of unstimulated sip-T, followed by CD19+ B-cells (4%, 1-82%), CD3-CD14-CD56+ natural killer (NK) cells (4%, 1-18%), and CD3-CD19-CD56-HLA-DR+CD11c+CD14+ monocytes (1%, 1-37%). Following sip-T stimulation with IL-15, a significant expansion and activation (increase in IFNγ+, CD95+, CD107+, and CD69+ cells) of CD8+ T-cell and NK cell populations was seen. A significant increase in signature cytokines (e.g. IFNγ and granulysin) in cell supernatants was also seen after IL-15 stimulation. Furthermore, IL-15 stimulated sip-T showed significantly higher cytotoxicity of LNCaP and DU145 cells in vitro. Adoptive transfer of IL-15 stimulated sip-T into LNCaP-bearing NSG mice resulted in significantly reduced tumor growth compared with those receiving untreated sip-T. Evaluation of tumor-infiltrating lymphocytes revealed a significant expansion of CD8 T-cell/NK populations and reduction in exhausted (PD1+, TIM3+) T-cell/NK cells in the IL-15-sip-T group compared to controls.

Conclusions: This is the first comprehensive study to evaluate the composition of sip-T from mCRPC patients using high dimensional CyTOF analysis, and serves as an important reference source for further modification and improvement of sip-T efficacy. Furthermore, our data is the first to show that the addition of IL-15 to sip-T could potentially enhance the efficacy of sip-T in mCRPC patients.