CD8-TARGETED IL-2 DRIVES POTENT ANTI-TUMOR EFFICACY AND PROMOTES ACTION OF TUMOR SPECIFIC VACCINES

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Background IL-2 and currently available engineered variants are of interest for solid tumor treatment, but their efficacy and toxicity profiles remain suboptimal. These results reflect the pleiotropic signaling via IL-2 receptors on different cell types that may simultaneously drive desired and undesired responses. We hypothesized that restricting IL-2's activity to CD8+ T cells would improve efficacy while also lowering its toxicity profile.

Methods We developed a cis-targeted IL-2 that selectively acts on CD8+ T cells (CD8-IL2) and assessed its activity using the T3 progressor MCA sarcoma model, which was selected because (a) it is sensitive to anti-PD-1 therapy when tumors are small but develops insensitivity as tumor size increase, (b) rejection requires both CD4+ and CD8+ T cells and (c) rejection is dependent on tumor expression of two neoantigens: mltgb1 (MHC-II) and mLama4 (MHC-I).

Results Whereas mice bearing 8-day T3 tumors had become insensitive to anti-PD-1 mediated tumor rejection, 90% of mice treated with single dose CD8-IL2 monotherapy rejected their tumors, while high dose IL-2 produced minimal efficacy. Efficacy occurred without body weight loss. These results suggest that CD8-IL2 can induce therapeutic effects at a time when tumors became insensitive to anti-PD-1. To assess this possibility in a more controlled manner, we used a tumor neoantigen vaccine model that depends on CD4+ T cell help for development of functional CD8+ T cells at both the priming stage in the lymph node as well as the effector stage at the tumor site. Mice bearing T3 tumors were vaccinated with a synthetic long peptide (SLP) containing the mLama4 neoepitope and either a high or low dose of an SLP containing the mltgb1 neoepitope. Whereas 85% of tumor bearing mice that received the vaccine containing mLama4 plus low dose mltgb1 SLP rejected their tumors, surprisingly none of the mice receiving high dose mltgb1 underwent tumor rejection. This high dose inhibition was reversed when CD8-IL2 was administered after high dose vaccination and at concentrations that had only modest activity in tumor bearing, non-vaccinated mice. With CD8-IL2 treatment, antigen specific T cells were expanded and displayed increased expression of activation-associated markers and reduced expression of exhaustion-associated markers.

Conclusions CD8-IL2 outperformed other forms of engineered IL-2 in anti-tumor efficacy, showed a significantly improved toxicity profile, and rescued deficient CD8 T cell responses resulting from poor CD4 help. In sum, we demonstrate high level antitumor efficacy and tolerability with a new form of targeted IL-2.

Ethics Approval Mice used in this study were between 8 and 12 weeks of age and were maintained in accordance with procedures approved by the Association for Assessment and Accreditation of Laboratory Animal Care and Accredited Animal Studies Committee of Washington University in St. Louis

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