A forced marriage of IL-2 and PD-1 antibody nurtures tumor-infiltrating T cells

Erin A. Holcomb, Weiping Zou

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Commentary

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A forced marriage of IL-2 and PD-1 antibody nurtures tumor-infiltrating T cells

Erin A. Holcomb and Weiping Zou

1Graduate Program in Immunology, 2Department of Surgery, and 3Department of Pathology, University of Michigan School of Medicine, Ann Arbor, Michigan, USA. 4Center of Excellence for Cancer Immunology and Immunotherapy, University of Michigan Rogel Cancer Center, Ann Arbor, Michigan, USA.

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Targeting IL-2 signaling pathway for cancer therapy
IL-2 is produced primarily by activated CD4+ T cells and acts in a paracrine or autocrine fashion (1, 2). IL-2 receptor (IL-2R) signaling occurs through three subunits: alpha (CD25), beta (CD122), and gamma (CD132) (3). Intermediate-affinity dimeric IL-2 receptor consists of IL-2Rβ and IL-2Rγ on naive CD4+ and CD8+ T cells, memory T cells, and natural killer (NK) cells. TCR engagement or IL-2 stimulation induces the expression of IL-2Ra to form high-affinity trimeric IL-2 receptors that are highly expressed on Treg cells and recently activated effector T cells (4). IL-2 signaling has been an attractive immunotherapeutic target since IL-2 mediates effector T cell activation, including effector CD8+ T cells, which are vital for antitumor immunity.

High-dose IL-2 was approved by the FDA in 1992 for treatment of certain types of cancer (5). However, IL-2 possesses a very short half-life and requires high doses to be effective, leading to toxicity and severe side effects, such as inflammation and vascular leak syndrome (6). Alternatively, low doses of IL-2 preferentially target IL-2Ra on Treg cells, restricting the immune response, and are associated with poor prognosis in patients with cancer (7, 8). Therefore, methods to target certain T cell subsets while reducing Treg cell binding have been a recent focus in the field of IL-2 therapy.

Manipulation of T cell phenotype by IL-2 therapy
To effectively manipulate effector T cells and reduce side effects of high-dose IL-2, IL-2 variants have been developed to stimulate specific T cell subsets through selective targeting of certain IL-2R chains. One strategy has been to introduce mutations in IL-2 to create mutants with preferential IL-2R chain binding. Mutants with reduced IL-2Rβ binding have been shown to target high-affinity IL-2 receptor expressed on effector T cells (Figure 1). These mutants have also exhibited reduced toxicity, possibly due to decreased binding of intermediate-affinity receptors on NK cells that lack IL-2Rα (1, 9). STK-012, a partial IL-2 agonist produced by Synthekine, employs a similar strategy by selectively binding IL-2Ra and IL-2Rβ subunits, but not IL-2Rγ. Effector T cells that may be specific for tumor epitopes can thus expand and readily attack the tumor while avoiding NK cell stimulation (10). However, undesirable Treg cell expansion remains a concern due to high IL-2Ra expression on Treg cells (7, 8). To address this issue, IL-2 mutants with reduced binding to IL-2Ra have also been generated. The cytokine company Nektar has engineered an IL-2 mutant with a bias toward IL-2Rβ and IL-2Rγ, rather than IL-2Ra, to reduce T cell binding (10). H9, an IL-2 superkine (sum-IL-2) with enhanced IL-2Rβ binding without the need for IL-2Ra, was shown to increase expansion of cytotoxic memory T cells and NK cells while decreasing that of Treg cells (11). Interestingly, H9T, an engineered H9-based partial agonist with further reduced binding to IL-2Ra, was also recently shown to promote CD8+ T cell proliferation that maintained a stem-like memory state and mediated greater antitumor immunity (12).

To enhance the activity of IL-2 in vivo and limit toxicity by reducing the necessary dose, IL-2 therapy has been combined with anti–IL-2 monoclonal antibodies (mAb). Interestingly, various anti–IL-2 mAbs differentially stimulate different immune cell subsets. Anti–mouse IL-2 mAbs S4B6 and JES6-5, as well as anti–human IL-2 mAb MAB602, complexed with recombinant IL-2, selectively stimulate memory CD8+ cells and NK cells in vivo to improve IL-2 cancer therapy (Figure 1) (13). On the other hand, anti–IL-2 mAb JES6-1 inhibits proliferation of CD8+ cells and NK cells yet maintains its ability to activate Treg cells and has been impli-
PD-1–laIL-2 seemed to selectively target intratumoral PD-1+TIM-3+CD8+ T cells, which are usually described as a functionally exhausted and/or terminally differentiated T cell subset. Therefore, PD-1–laIL-2 could reactivate PD-1+TIM-3+CD8+ T cells to enhance antitumor activity (Figure 1). Tumor rechallenge resulted in spontaneous rejection in tumor-bearing mice previously treated with PD-1–laIL-2. This effect was also dependent on the presence of CD8+ T cells, indicating these rejuvenated T cells are tumor antigen-specific and can mediate a strong memory response. These promising results suggest that PD-1–laIL-2 therapy may bring clinical benefits to patients with cancer.

Address correspondence to: Weiping Zou, Departments of Surgery and Pathology, University of Michigan Medical School, 109 Zina Pitcher Place, Ann Arbor, Michigan 48109, USA. Phone: 734.763.6402; Email: wzou@med.umich.edu.

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