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Commentary

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

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IL-2 is a pleiotropic cytokine. In this issue of the JCI, Ren et al. report on the development of a low-affinity IL-2 paired with anti–PD-1 (PD-1–ilaL2) that reactivates intratumoral CD8+ T cells, but not CD4+ Treg cells. PD-1–ilaL2 treatment synergized with anti–PD-L1 therapy to overcome tumor resistance to immune checkpoint blockade (ICB) in tumor-bearing mice. Rejection of rechallenged tumors following PD-1–ilaL2 therapy demonstrated the establishment of a potent T cell memory response. Furthermore, PD-1–ilaL2 therapy manifested no obvious toxicity. These findings suggest the potential of PD-1–ilaL2 therapy in treating patients with cancer.

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-2Rα 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-2Rα 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-2Rα 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-2Rα expression on Treg cells (7, 8). To address this issue, IL-2 mutants with reduced binding to IL-2Rα 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-2Rα, to reduce Treg cell binding (10). H9, an IL-2 superkine (sum-IL-2) with enhanced IL-2Rβ binding without the need for IL-2Rα, 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-2Rγ, 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, complexes 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.

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