1236 SELECTIVE DELIVERY OF LOW-AFFINITY IL-2 TO PD-1+ T CELLS REJUVENATES ANTITUMOR IMMUNITY WITH REDUCED TOXICITY

[1]Zhenhua Ren*, [2]Anli Zhang, [2]Yang-Xin Fu. [1]*Changping Laboratory, Beijing, China*; [2]*UT Southwestern Medical Center, Dallas, TX, USA*

Background Increased levels of tumor-infiltrating lymphocytes (TILs) are associated with improved survival in patients with cancer. Anti–PD-1/PD-L1–based cancer immunotherapies have revolutionized the treatment of cancers, and TIL abundance can be used as a prediction marker for immunotherapy responsiveness. Even though PD-1/PD-L1 blockade can release the brake on the T cell response, T cells are not fully functional and are limitedly expanded in the tumor. Most patients either fail to respond or develop adaptive resistance after an initial response. Importantly, the role of T cell–associated cytokines in the tumor microenvironment for anti–PD-1/PD-L1 responsiveness has not been fully studied. It is possible that additional T cell–driven cytokine therapy might overcome PD-1 therapy resistance. IL-2 is an important T cell growth factor for T cell proliferation. How to target IL-2 to tumor-specific T cells remains a challenge in IL-2 cancer immunotherapy.

Methods Here, we designed a fusion protein (IL-2 linked to an anti–PD-1 antibody) to target TILs, as TILs express more PD-1 than other cells. To reduce the binding of IL-2 to Tregs, we selected a lowaffinity IL-2 (laIL-2) that has greatly reduced binding to both IL-2Rα and IL-2Rβ. We linked laIL-2 to an anti–PD-1 antibody (generating PD-1–laIL-2) to increase its avidity to intratumoral CD8+ T cells.

Results We fortuitously observed that anti–PD-1 therapy depends on IL-2 signaling, which raises the possibility that a lack of IL-2 limits anti–PD-1–induced effector T cell expansion. To selectively deliver IL-2 to PD-1+CD8+ tumor-infiltrating lymphocytes (TILs), we engineered a low-affinity IL-2 paired with anti–PD-1 (PD-1–laIL-2), which reduced affinity to peripheral Treg cells but enhanced avidity to PD-1+CD8+ TILs. PD-1–laIL-2 exerted better tumor control and lower toxicity than single or mixed treatments. Mechanistically, PD-1–laIL-2 could effectively expand dysfunctional and tumor-specific CD8+ T cells. Furthermore, we discovered that presumably dysfunctional PD-1+TIM3+ TILs are the dominant tumor-specific T cells responding to PD-1–laIL-2.

Conclusions Collectively, these results highlight that PD-1–laIL-2 can target and reactivate tumor-specific TILs for tumor regression as a unique strategy with stronger efficacy and lower toxicity.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1236