Abstract

Biological activity of IL-2 and IL-7 *in vivo* is significantly increased when complexed with some of the respective anti-cytokine mAb. Different immune cell subsets can be preferentially stimulated depending on the anti-IL-2 mAb used to complex IL-2. IL-2/anti-IL-2 mAb S4B6 immunocomplexes (IL-2/S4B6) induce preferential expansion of $CD122^{high}$ cells whereas IL-2/anti-IL-2 mAb JES6-1 immunocomplexes (IL-2/JES6-1) highly selectively stimulate $CD25^{high}$ cells in mice. Similarly, IL-7/anti-IL-7 mAb M25 immunocomplexes (IL-7/M25) possess higher stimulatory activity for both naïve and memory $CD8^+$ T cells *in vivo* in comparison to free IL-7. CTLA-4 and PD-1 molecules are inhibitory receptors which negatively regulate proliferation, survival and effector functions of T cells. Blocking antibodies against these molecules represent promising immunotherapeutic tool for treatment of malignant diseases.

We examined possible synergism of IL-2/S4B6 and αCTLA-4 plus αPD-1 mAbs in tumor-bearing mice. We found that the expansion of recently activated $CD8^+$ T cells driven by IL-2/S4B6 was further augmented by αCTLA-4 plus αPD-1 mAbs. However, these two immunotherapeutic approaches did not show synergistic antitumor activity in any mouse tumor model tested.

Next, we showed that IL-7/M25 possessed higher biological activity in terms of stimulation of proliferation of $CD4^+$ and $CD8^+$ T and B cells *in vivo* in comparison to free IL-7. Moreover, IL-7/M25 had no stimulatory activity for Tregs. We thus tested possible antitumor activity of IL-7/M25 in combination with αCTLA-4 plus αPD-1 mAbs. Unexpectedly, IL-7/M25 but not free IL-7 dampened the antitumor activity of αCTLA-4 plus αPD-1 mAbs in all tested mouse tumor models. This paradoxical effect of IL-7/M25 is not mediated via TGF-β or IL-10 production.

Key words

IL-2, IL-7, IL-2/S4B6 immunocomplex, IL-2/JES6-1 immunocomplex, IL-7/M25 immunocomplex, αCTLA-4 and αPD-1 blocking mAbs, tumor immunotherapy