CD24Fc AMELIORATES IMMUNE-RELATED ADVERSE EVENTS WHILE PRESERVING ANTI-TUMOR THERAPEUTIC EFFECT

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Background Combination therapy with anti-CTLA-4 and anti-PD-1 mAbs has emerged as the most potent and durable cancer immunotherapy, yet it is associated with frequent and severe immune-related adverse events (irAEs).¹⁻² A largely unmet medical need is to reduce irAEs. The CD24–Siglec 10/G interaction is an emerging immune checkpoint that regulates inflammation caused by danger-associated molecular patterns (DAMPs).³⁻⁵ It is of great interest to investigate whether CD24Fc can ameliorate severe irAEs, the hallmark of which is a severe inflammatory state in multiple organs.

Methods We used a human CTLA-4 knock-in (Ctla4h/h) mice model that fully recapitulates human irAE in response to anti-PD-1 and anti-CTLA-4 antibodies to test if CD24Fc have therapeutic effect for irAE. We treated Ctla4h/h mice with Ipilimumab and anti-PD-1 Ab in conjunction with hIgFc or CD24Fc on day 10, 13, 16 and 19 after birth. The body weight was monitored over time, hematologic and histopathologic alterations were evaluated at 6 weeks of age. To evaluate the therapeutic effect of CD24Fc on ICIs induced tissue destruction, we performed histological analysis of internal organs and glands. Major organs were collected about 1 month after first treatment and fixed in 10% formalin, sectioned and stained with hematoxylin and eosin (H&E), and scored double blindly. To test whether CD24Fc immune modulation may interfere with the anti-tumor efficacy of the checkpoint inhibitors, we inoculated MC38 and B16-F10 tumor cells on Ctla4h/h mice, then treated with combination of Ipilimumab and anti-PD-1 Ab together with hIgFc or CD24Fc and monitored tumor growth.

Results We found that anti-CTLA-4 and anti-PD-1 therapy could induce growth retardation, anemia and severe inflammation in all organs examined. All of these adverse events were ameliorated by CD24Fc treatment. Moreover, in both tumor models tested CD24Fc modestly enhanced immunotherapeutic effect of anti-PD-1 and anti-CTLA-4 antibodies. CD24Fc treatment showed no effect on CD4+, CD8+ T cell or tumor associated macrophage (TAM) density intratumor. However, we observed significantly decreased Treg among CD4+T cells after CD24Fc treatment. CD24Fc treatment also decreased the TIM-3+ PD-1+ CD4+ and CD8+ T cells. These data suggest CD24Fc has the potential to optimize tumor microenvironment and augment antitumor immunity.

Conclusions Our data demonstrate that CD24Fc treatment ameliorates irAEs in multiple organs induced by combination of anti-CTLA-4 and anti-PD-1 Abs while modestly enhancing its anti-tumor activity, potentially by reducing the intratumor regulatory T cells and reverse exhaustion of tumor-infiltrating T cells.

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