Combined anti-PD-1 and anti-LAG-3 checkpoint blockade enhances CD8+ TIL effector function while reducing Tregs leading to reduced immune suppression and improved overall survival

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Combined anti-PD-1 and anti-LAG-3 checkpoint blockade enhances CD8+ TIL effector function and improves overall survival

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Introduction

Checkpoint inhibition is a potent strategy to reinvigorate T cells. However, aCTLA-4 or aPD-1 monotherapy has not been effective for the majority of patients, resulting in the exploration of combinatorial approaches to improve treatment efficacy. One such target is LAG-3, which is upregulated on T cells that have experienced repeated antigen exposure, such as in the tumor microenvironment (TME), and is associated with reduced T cell effector function. In addition, high LAG-3 expression on regulatory T cells (Tregs) has been reported for patients with varying cancer types, providing an additional rationale for targeting LAG-3 with the aim of reducing immune suppression within the TME. We hypothesized that the combination of aPD-1 and aLAG-3 would synergize to promote tumor regression and increase survival via a reduction in tumor-induced immune suppression and enhanced CD8+ T cell effector function.

Methods

CT26 colon carcinoma

BALB/c

10x10^6 CT26 cells were implanted in the flank of BALB/c mice. For survival experiments, tumors were measured 2x/week and mice were sacrificed when tumors were >150mm^2. For TIL analysis, tumors were digested and immune cells analyzed by flow cytometry. Statistics were analyzed by one-way ANOVA. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Tumor Growth and Survival

Figure 1. Dual aPD-1/aLAG-3 blockade enhances tumor regression and survival. CT26 cells were implanted in BALB/c mice (day 0). Tumor-bearing mice were treated with aPD-1 and/or aLAG-3 mAbs (days 7, 10, 13; 10 mg/kg, ip). Tumor growth (area; mm^2) was measured 2x/week and mice were sacrificed when tumors were >150mm^2.

Figure 2. Dual aPD-1/aLAG-3 blockade enhances CD8+ TIL effector function. A-D) CT26 tumor-bearing mice were treated as in Fig 1. B) Predicted responders (R) were determined by an overall reduction in tumor size (d7-d17), non-responders (NR) had a net increase in tumor size. C-D) Day 17, tumors were harvested for analysis by flow cytometry.

Conclusions

- aPD-1/aLAG-3 therapy enhances tumor regression and survival
- Responders to dual therapy display increased CD8+ T effector function: Ki-67, GzmA, TNFα, & IFNγ
- Treg & Teff populations: Increased proliferation & expression of LAG-3 correlate with response
- Dual aPD-1/aLAG-3 increases myeloid expression of PD-L1
- CD8 depletion abrogates effects of dual therapy; CD4 depletion dramatically increases survival

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