LAIR-1 INHIBITION ENHANCES ANTI-PD-1 EFFICACY

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Background Leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1) is an immune inhibitory collagen-binding receptor that is aberrantly expressed in tumors. Recent work by others has led to conflicting views of immunoinhibitory versus immunoenhancing roles for LAIR-1 in solid tumors. Here, using well-defined syngeneic mouse tumor models, we assess the antitumor efficacy of LAIR-1 inhibition/depletion either alone or in combination with anti-PD-1.

Methods To evaluate the effect of LAIR-1 inhibition on in vivo tumor growth and control, we used either Lair1–/– mice or a LAIR-1 blocking monoclonal antibody (mAb). We used two antigenically distinct MCA-induced C57Bl/6 strain sarcoma lines (1956 and 7347), a 129S6 strain sarcoma line (F244) and a PD-1 sensitive clone of C57Bl/6 MC38 (MC38-5s). To assess the effects of LAIR-1 deficiency on tumor immunity, we injected either 1956, 7347, or MC38-5s cells into either syngeneic Lair1–/– or WT mice, and 10 days later, when tumor-bearing WT mice became insensitive to anti-PD-1 therapy, initiated either anti-PD-1 or Ctrl mAb therapy. To evaluate the efficacy of LAIR-1 blocking mAb as monotherapy or in combination with anti-PD-1, we treated 1956 or 7347 bearing WT C57Bl/6 mice and F244 bearing WT 129S6 mice continuously with either anti-LAIR-1 or Ctrl mAb. Ten-days after tumor inoculation, mice were additionally treated with either anti-PD-1 or Ctrl mAb.

Results Whereas 89% of anti-PD-1 treated Lair1–/– mice rejected 1956 sarcomas, only 22% of Ctrl mAb treated Lair1–/– mice and 6% of anti-PD-1 treated WT mice rejected their tumors. PD-1 blockade of Lair1–/– mice bearing 7347 sarcomas or MC38-5s tumors induced similar rejection responses. In WT mice, the anti-LAIR-1 and anti-PD-1 combination induced better anti-tumor efficacy than anti-LAIR-1 or anti-PD-1 monotherapy. Flow cytometry analysis revealed that tumor-specific T cells were significantly increased in anti-PD-1 treated Lair1–/– mice compared to anti-PD-1 treated WT mice. Depletion of CD4+ and/or CD8+ T cells in Lair1–/– mice inhibited anti-PD-1 mediated tumor rejection. High dimensional profiling via CyTOF analyses of the myeloid cell compartment from 1956 tumors in Lair1–/– mice treated with either anti-PD-1 or Ctrl mAb revealed a selective increase over similarly treated WT mice in a macrophage cluster expressing CD206 and folate receptor-b, suggesting that development of this macrophage cluster was LAIR-1 dependent.

Conclusions This study shows that inhibition of LAIR-1 in tumor bearing mice sensitizes advanced tumors to anti-PD-1 treatment.