BATF3 DENDRITIC CELLS AND 4-1BB/4-1BB LIGAND AXIS ARE REQUIRED AT THE EFFECTOR PHASE WITHIN THE TUMOR MICROENVIRONMENT FOR ANTI-PD-L1 EFFICACY

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Background PD-1/PD-L1 blockade has shown clinical benefit across many cancer types. However, a large fraction of patients are resistant to immune checkpoint blockade therapy and others eventually relapse. Understanding the mechanisms involved in α PD1/PD-L1 immunotherapy efficacy may enable new strategies for improving clinical outcomes. Given that Batf3-lineage dendritic cells (DCs) are needed for spontaneous T cell priming in the tumor-draining lymph node and for recruitment of effector CD8⁺ T cells to the tumor, in the current work we examined whether Batf3⁺ DCs are also required during the effector phase of the anti-tumor immune response at the time of anti-PD-L1 administration for therapeutic efficacy.

Methods We utilized the B16-SIY melanoma model, CD11c-DTR-GFP, and CD11c-DTR-GFP/Batf3 KO bone marrow chimeras to study the role Batf3⁺ DCs play during anti-PD-L1 immunotherapy. To focus on the effector phase of the immune response, we depleted CD11c⁺ cells with diphtheria toxin from day seven of tumor injection while simultaneously blocking new T cell entry with FTY720. As flow cytometry revealed high 4-1BBL expression on intratumoral Batf3-DCs, 4-1BB KO mice and anti-4-1BBL blocking antibodies were used. Tumor growth and phenotypic analysis of the tumor infiltrate were evaluated.

Results Strikingly, we observed that CD11c⁺ cells, and specifically Batf3⁺ DCs, were required in the tumor prior to α PD-L1 treatment for immunotherapy efficacy. The normal intratumoral expansion of antigen (Ag)-specific CD8⁺ tumor-infiltrating T cells (TILs) and increased ratio between Ag-specific CD8⁺ TILs and regulatory T cells following anti-PD-L1 therapy was eliminated with Batf3⁺ DC depletion. Batf3⁺ DCs expressed high levels of 4-1BBL, and increased expression of 4-1BB on antigen-specific CD8⁺ TILs upon α PD-L1 treatment required Batf3⁺ DCs. Mechanistic experiments confirmed a requirement for 4-1BB expression on immune cells for α PD-L1 efficacy, and blocking antibodies against 4-1BBL eliminated anti-PD-L1 efficacy as well. Using appropriate bone marrow chimeras, agonistic 4-1BB antibodies were sufficient to bypass the need for CD11c⁺ DCs at the effector phase for tumor control. In human melanoma samples, co-localization of Batf3⁺ DCs and CD8⁺ T cells was observed in T cell-inflamed tumors, which correlated with anti-PD-1 efficacy in metastatic melanoma.

Conclusions Our results indicate that Batf3⁺ DCs are necessary during the effector phase of the anti-tumor immune response for anti-PD-L1 efficacy to occur, at least in part through 4-1BB/4-1BBL-mediated reinvigoration of Ag-specific CD8⁺ TILs.

Ethics Approval The study obtained ethics approval, IRB protocol 15-0837.

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