PULMONARY PRIMING OF TUMOR-REACTIVE CD8⁺ T CELLS BY DC1 IS IMPAIRED BY REGULATORY T CELLS

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Background Although failure to respond to checkpoint blockade immunotherapies (CBT) is frequently associated with a lack of T cell infiltration into the tumor, emerging clinical data suggests that specifically in patients with lung cancer, T cell-inflamed tumors can also be resistant to therapy.¹ Recent work by our group identified that immunotherapy resistance in a T cell-inflamed pre-clinical mouse model of lung cancer is driven by a lung cancer-specific CD8⁺ T cell dysfunctional program (Tₐdys), characterized by blunted production of IFNγ and reduced cytolytic capacity. Intriguingly, this Tₐdys program is established during priming in the tumor-draining mediastinal lymph nodes (mLN). Understanding the lung-specific mechanisms blunting the activation of anti-tumor T cell responses could enable development of novel therapies needed to improve outcomes of patients with CBT-resistant T cell-inflamed lung cancer.

Methods To study anti-tumor immune responses against lung tumors, a syngeneic lung cancer cell line (KP) was implanted orthotopically or subcutaneously into C57BL/6 mice. KP cells were engineered to express SIINFEKL and ZsGreen to enable studies of tumor-reactive T cells and antigen uptake by dendritic cells (DC).

Results Lung KP tumors led to the induction of tumor-reactive Tₐdys CD8⁺ T cells lacking CD25 and GzmB in the mLN, in contrast to subcutaneous KP tumors, which induced CD25⁺GzmB⁺ tumor-reactive CD8⁺ T cells in the inguinal LN (iLN). Mouse models lacking DC1 revealed that DC1 are necessary to prime tumor-reactive CD8⁺ T cells in both LNs. Flow cytometry characterization of DC1 from LNs revealed equivalent levels of antigen load, but reduced levels of costimulatory molecules CD80, CD86 and the cytokine IL-12 in the mLN compared to iLN, suggesting a blunted stimulatory capacity in the lung setting. Regulatory T cell (Treg) depletion using FoxP3DTR mice rescued expression of effector T cell priming in tumor-draining mLN, suggesting that Tₐdys induction requires the presence of local Treg. Ex vivo co-cultures of antigen-specific CD8⁺ T cells with DC1 and Treg sorted from the mLN fully recapitulated the in vivo observation, suggesting that both DC1 and Treg are required and sufficient for Tₐdys induction. Blockade of the MHCII-dependent DC1:Treg interaction restored an effector-like profile of tumor-reactive CD8⁺ T cells.

Conclusions Treg restrain DC1 stimulatory function in the tumor-draining mLN, leading to the induction of lung cancer-specific dysfunction in tumor-reactive CD8⁺ T cells and thus rendering the T cell response refractory to CBT-mediated reinvigoration. Blockade of Treg:DC1 interactions can restore priming of lung cancer-reactive effector T cell responses.

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REFERENCE

Ethics Approval All mouse experiments in this study were approved by MIT’s Committee on Animal Care (CAC) - DHHS Animal Welfare Assurance # D16-00078

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