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 (T_{Ldys}), characterized by blunted production of IFN γ and reduced cytolytic capacity. Intriguingly, this T_{Ldys} 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 T_{Ldys} CD8⁺ T cells lacking CD25 and GzmB in the mLN, in contrast to subcutaneous KP tumors, which induced CD25^{high} GzmB^{high} 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 FoxP3^{DTR} mice rescued expression of effector T cell priming in tumor-draining mLN, suggesting that T_{Ldys} 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 T_{Ldys} 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

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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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