

DENDRITIC CELL-INTRINSIC PTPN22 NEGATIVELY REGULATES ANTI-TUMOR IMMUNITY

Santiago Acero-Bedoya*, Emily Higgs, Anna Martinez, Thomas Gajewski. *University of Chicago, Chicago, IL, United States*

Background Checkpoint blockade immunotherapies have revolutionized cancer treatment, yet only a subset of patients benefit. Individuals with a loss-of-function single nucleotide polymorphism in the gene encoding PTPN22 are at increased risk for autoimmune disease and display a lower incidence of certain cancers. Studies in PTPN22 knockout (KO) mice have established it as a negative regulator of T cell responses in autoimmune and cancer models. However, these studies have not defined the cell lineage-intrinsic roles of PTPN22 in distinct immune cell compartments, and the potential role of PTPN22 in dendritic cells remains undefined.

Methods We developed a novel dendritic cell (DC) PTPN22 conditional KO (cKO) mouse model that enables specific deletion in CD11c⁺ cells. Using the B16.SIY melanoma model, tumor growth and immune profiles of tumors and tumor-draining lymph nodes (tdLNs) were analyzed. CD8⁺ T cells were depleted to establish their necessity using an anti-CD8b monoclonal antibody. Antigen-specific T cell priming was tested by IFN- γ ELISpot analysis on the spleens of tumor-bearing mice. Lastly, the MC38.SIY cell line was used to establish the applicability in different cancer models.

Results Deletion of PTPN22 in DCs resulted in augmented tumor control. At endpoint, total CD8⁺ T cells, but not CD4⁺ T cells or Tregs, were increased in the tumors of CD11c⁺ PTPN22 cKO mice. Moreover, CD8⁺ T cells demonstrated increased activation and memory markers at day 10 in the tdLN and in day 27 tumor-infiltrating lymphocytes. Depleting CD8⁺ T cells eliminated the tumor growth control in this model, suggesting a reliance on the DC-CD8⁺ T cell axis. Accordingly, day 7 tumor-bearing mice revealed an increased frequency of IFN- γ -producing T cells in the presence of tumor antigen SIY, indicating improved CD8⁺ T cell priming. Further, spectral analysis of tumor antigen-specific T cells in the tdLN also showed a significant increase of CD8⁺ SIY⁺ T cells displaying elevated activation and memory markers. Analysis of DCs in the tdLN similarly revealed an overall increase attributed to an increase of CD103⁺, but not CD11b⁺, DCs displaying increased activation and proliferation markers. Together, the number of tumor-infiltrating CD8⁺ T cells and CD103⁺ DCs correlated with decreased tumor volumes. Lastly, PTPN22 cKO mice similarly showed greater tumor control of the colon cancer line MC38.SIY.

Conclusions We show that deletion of PTPN22 in DCs is sufficient to drive a tumor antigen-specific T cell response resulting in enhanced tumor control. This work highlights the potential to modulate anti-tumor immunity through the manipulation of DC signaling.

Ethics Approval This study obtained ethics approval by the Institutional Animal Care and Use Committee (IACUC) at the University of Chicago as outlined in the animal protocol #71621.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0978>