

DENDRITIC CELL-INTRINSIC PTPN22 NEGATIVELY REGULATES ANTI-TUMOR IMMUNITY AND IMPACTS ANTI-PD-L1 EFFICACY

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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 have increased risk for autoimmune diseases, and cancer patients with such alleles may respond better to checkpoint blockade immunotherapy. Studies in PTPN22 knockout (KO) mice have established it as a negative regulator of T-cell responses in cancer models. However, the role of PTPN22 in distinct immune cell compartments, such as dendritic cells (DCs), remains undefined.

Methods We developed a novel DC PTPN22 conditional KO (cKO) mouse model that enables specific deletion in CD11c⁺ cells. Using the B16.SIY and MC38.SIY cancer models, tumor growth and immune profiles of tumors and tumor-draining lymph nodes (tdLNs) were analyzed. CD8⁺ T-cells were depleted 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. DC phenotypes and functionality were assessed particularly in the tumor microenvironment. Anti-PD-L1 antibody was used to test synergy between checkpoint blockade and DC PTPN22 deletion.

Results Deletion of PTPN22 in DCs resulted in augmented tumor control. CD8⁺ T-cells, but not CD4⁺ T-cells or Tregs, were increased in the tumors of CD11c⁺ PTPN22 cKO mice. Depleting CD8⁺ T-cells eliminated the tumor growth control, suggesting a reliance on the DC-CD8⁺ T-cell axis. Accordingly, day 7 tumor-bearing mice revealed an increase in IFN- γ -producing SIY-specific T-cells, indicating improved CD8⁺ T-cell priming. Analysis of tumor antigen-specific T-cells in the tdLN showed a significant increase of CD8⁺ SIY⁺ T-cells displaying elevated activation and memory markers. Likewise, there was an overall increase in CD103⁺ DCs displaying increased activation markers in the tdLN. Together, the number of tumor-infiltrating CD8⁺ T-cells and CD103⁺ DCs correlated with decreased tumor volumes. Intratumoral DCs showed significantly higher Ki67⁺ versus activated Caspase-3⁺ cells, which led to greater uptake of tumor-derived material in situ. PTPN22 cKO mice also showed greater tumor control of the colon cancer line MC38.SIY with an additional decrease in tumor growth and increased survival when treated with anti-PD-L1 therapy.

Conclusions Deletion of PTPN22 in DCs is sufficient to drive an augmented tumor antigen-specific T-cell response resulting in enhanced tumor control. Mechanistically, this is linked to a shift towards proliferating over apoptosing CD103⁺ DCs, leading to enhanced antigen presentation to CD8⁺ T-cells in vivo. This work argues that PTPN22 is likely regulating DC proliferative signals and highlights the potential to modulate anti-tumor immunity through the manipulation of DC signaling.

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