LOSS OF PD-1 SIGNALS IMPROVES CD8+ TIL FUNCTION IN A CELL INTRINSIC AND CELL EXTRINSIC MANNER

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Background Blockade of PD-1 or its ligand PD-L1 has led to improved clinical outcomes in diverse cancer types, and has been approved by the FDA for use in over 20 different advanced stage cancers. Though PD-1 pathway inhibitors show great promise, the mechanisms contributing to protective anti-tumor immunity following loss of PD-1 signaling remain incompletely understood.

Methods To elucidate the cell intrinsic consequences of PD-1 loss, as well as the impact of this loss on neighboring PD-1-expressing cells, we developed an inducible PD-1 knockout (KO) model whereby PD-1 could be deleted on roughly half of the CD8+ T cell population.

Results Using paired single cell RNA seq and TCR seq, we found that PD-1-expressing CD8+ T cells in the tumor received much of the same therapeutic benefit as those T cells lacking PD-1. Thus, many of the anti-tumoral changes that occurred in the CD8+ TIL population were not dependent on a cell intrinsic loss of PD-1, but instead were shared between cells that do or do not express PD-1.

Conclusions These data suggest that PD-1 inhibitors can act beyond each individual cell that they contact to promote a heightened anti-tumor state, and can impact T cell functions independent of direct PD-1 blockade.

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