Role of PD-1 in regulatory T cells in tumor microenvironment

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Regulatory T cells (Tregs) have an immunosuppressive function and highly express PD-1 in the tumor microenvironment (TME); however, the function of PD-1 in tumor-infiltrating (TI) Tregs remains controversial. Here, we first demonstrated that Treg-specific PD-1 conditional knockout mice were resistant to tumor progression. Capitalizing on PD-1 hetero mice in which both PD-1-intact and PD-1-deficient Tregs coexisted in the same tissue environment, we found that PD-1 ablation in Tregs resulted in impairment of the proliferative capacity and functionality of TI Tregs. We also found that PD-1 therapy was effective by reducing the TI Treg pool rather than directly restoring TI CD8+ T cell functionality. Single-cell analysis revealed that PD-1 signaling promoted lipid metabolism as well as proliferation and suppressive pathways in TI Tregs. These results suggest that PD-1 ablation or inhibition can enhance antitumor immunity by weakening Treg stability and metabolic fitness in the TME.