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Blockade of Treg derived TGF-β abrogates suppression of effector T cell function within the tumor microenvironment

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Regulatory T cells (Treg) play a role in suppression of anti-melanoma immunity; however, the exact mechanism is poorly understood. Through intravital two photon microscopy, we found that Pmel-1 effectors engage in cell-cell interactions with tumor resident Tregs. To determine if contact between Tregs and T effectors (Teff) hinders killing of tumor cells in vivo, we utilized ex-vivo three-dimensional collagen-fibrin gel cultures of B16 melanoma cells. Collagen-fibrin gel cultures recapitulated the in vivo suppression, rendering the dissociated tumor resistant to killing by in vitro activated antigen specific Teff. In vivo depletion of Tregs in foxp3-DTR mice prior to tumor excision reversed the suppression. Additionally, In vivo modulation of intra-tumor Tregs suppressive function by GITR ligation had a similar effect, leading to ex-vivo tumor killing. Using neutralizing antibodies, we found that blocking TGF-β reversed the suppression. In addition, soluble factors from collagen-fibrin gel tumors do not inhibit killing suggesting that suppression is contact or proximity dependent. The CD8 Teff recovered from these gels exhibit a decrease in Granzyme B expression and an increase in expression of T cell exhaustion marker PD-1. These findings support the conclusion that intra-tumor contact with Tregs during the effector phase of the immune response is responsible for inhibiting anti-melanoma immunity in a TGF-β dependent manner, elucidating a novel way to target intratumoral Tregs.

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