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T cell receptor affinity and avidity defines antitumor response and autoimmunity in T cell immunotherapy

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T-cells have evolved the unique ability to discriminate "self" from "non-self" with high sensitivity and selectivity. However, tissue-specific autoimmunity, tolerance or eradication of cancer does not fit into the self/non-self paradigm because the T-cell responses in these situations are most often directed to non-mutated self-proteins. To determine the TCR affinity threshold defining the optimal balance between effective antitumor activity and autoimmunity in vivo, we used a novel self-antigen system comprised of seven human melanoma $gp100_{209-217}$-specific TCRs spanning physiological affinities (1 to 100 μM). We found that in vitro and in vivo T cell responses are determined by TCR affinity. Strikingly, we found that T cell antitumor activity and autoimmunity are closely coupled but plateau at a defined TCR affinity of 10 μM, likely due to diminished contribution of TCR affinity to avidity above the threshold. Our results suggest a relatively low affinity threshold is necessary for the immune system to avoid self-damage given the close relationship between antitumor activity and autoimmunity. This, in turn, indicates that treatment strategies focusing on TCRs in the intermediate affinity range (KD ~10 μM) or targeting or targeting shared tumor antigens would dampen the potential for autoimmunity during adoptive T cell therapy for the treatment of cancer.

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