Anti-CCR8 mediates long-lasting antitumor immunological memory and enhances anti-tumor immunity in immune-cold cancer through the combination with chemotherapy

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Abstract Content:

Tumor infiltrating regulatory T cells (Tregs) suppress CD8+ T cells and facilitate tumor progression. Tumor Tregs are elevated in a variety of malignancies and have been associated with poor prognosis. Targeting Tregs presents an appealing strategy in cancer immunotherapy. Recent research has identified the chemokine receptor CCR8 is preferentially expressed by tumor Tregs and labels highly suppressive Tregs. Thus, using anti-CCR8 mAb to deplete tumor Tregs could be an efficient and safe strategy that is widely being explored.

Although the anti-tumor efficacy of CCR8 mAb was reported, the dynamics and specific contributions of Tregs and CD8+ T cells to anti-tumor activity are still not fully elucidated. We herein found that tumor Tregs were depleted quickly, within two days, while CD8+ T cells increased after one week upon treatment with anti-CCR8 in both MC38 and CT26 models. Tumor volume and weight have been found to be well-correlated with the numbers of CD8+ T cells, suggesting that the increased infiltration of CD8+ T cells may be indicative of an active anti-tumor immune response.

Furthermore, treatment with CCR8 mAb has shown dose-dependent efficacy in controlling the growth of CT26 tumor. In the 1 mg/kg dosage group, 3 out of 10 mice exhibited a complete response (CR), while in the 3 mg/kg dosage group, 4 out of 10 mice achieved a CR. Rechallenging the mice with 50-fold more tumor cells on the contralateral side of the CR mice still resulted in the expulsion of tumor growth without any treatment, suggesting that the use of CCR8 mAb induces a long-lasting antitumor immunological memory. This is crucial for maintaining persistent tumor immune surveillance and achieving durable responses to cancer therapy. This finding underscores the potential of CCR8 mAb not only in directly targeting tumor growth but also in bolstering the host's immune memory, contributing to a more comprehensive and enduring antitumor defense.

In addition, further improved tumor growth inhibition was observed when combining anti-CCR8 with docetaxel, oxaliplatin, or gemcitabine in immune cold tumor models. PD analysis revealed that the combination of CCR8 mAb therapy with gemcitabine induced the depletion of Tregs, increase of CD8+ T cells, decrease of tumor-associated macrophages, and the activation of DCs, which are instrumental in treating immune-cold tumors. This suggests that the combined therapy may enhance the antitumor immune response by modulating the tumor microenvironment, thereby improving the efficacy of cancer treatment.

Collectively, these findings advance our understanding of CCR8 as a promising target for Treg depletion in anti-cancer drug development and therapy.