Medical & healthcare, Drug development

Development of a novel cancer immunotherapy by targeting regulatory T cells

Department of Frontier Research in Tumor Immunology, Graduate School of Medicine

Specially Appointed Professor Naganari Ohkura

Researchmap https://researchmap.jp/read0007148?lang=en

Abstract

Regulatory T cells (Tregs) are essential for immune homeostasis and maintain homeostasis by negatively regulating excessive immune responses. Because of this property, removal of Tregs is thought to be effective in strengthening cancer immunity, yet at the same time, there is concern that it may also increase the risk of autoimmune diseases. Therefore, in order to induce strong anti-tumor immunity while avoiding autoimmune diseases, we attempted to selectively remove tumor-infiltrating Tregs. First, we identified the chemokine receptor CCR8 as a molecular target specific to tumor-infiltrating Tregs. In tumor-bearing mouse models, CCR8-targeted Treg removal demonstrated strong anti-tumor immunity while avoiding autoimmune diseases. Furthermore, in these individuals, long-term anti-tumor immune memory was also established. Based on these results, we have developed a human anti-CCR8 antibody, and are now conducting a clinical trial of the antibody against solid tumors.

Background & Results

Regulatory T cells (Treg) are essential for immune homeostasis and maintain homeostasis by negatively regulating abnormal or excessive immune responses. This characteristic of Tregs makes their control effective in suppressing autoimmune diseases, and in enhancing cancer immunity. Therefore, we attempted to develop a new therapy for cancers by focusing the diversity of Tregs.

Previous studies have shown that Treg removal can enhance anti-tumor immune activity. However, since systemic Treg removal can cause severe autoimmune diseases, its application to cancer therapy requires a trick to enhance only anti-tumor immune activity while avoiding the onset of autoimmune diseases. One possible solution to the problem is cell removal targeting only tumor-infiltrating Tregs. Therefore, we searched for cell surface molecules that are specific to tumor-infiltrating Treg cells. Single-cell analysis of tumor-infiltrating T cell fractions isolated from human clinical specimens revealed the chemokine receptor CCR8 as a membrane surface molecule with high specificity for tumor-infiltrating Treg cells. In tumor-bearing mouse models, administration of anti-CCR8 antibody demonstrated potent anti-tumor immune activity while evading autoimmune disease. Furthermore, in about half of these individuals, complete elimination of cancer was achieved, and long-term anti-tumor immune memory was also established. These results indicate that selective elimination of Tregs may become a new cancer immunotherapy. We are now conducting a clinical trial of a human anti-CCR8 antibody against several solid tumors.

Significance of the research and Future perspective

Cancer immunotherapy has been established as the fourth therapeutic modality, but its response rate is still low and its application is limited depending on the cancer types. On the other hand, anti-CCR8 antibody has shown broad efficacy against various solid tumors in tumor-bearing mouse models, and the synergistic effects with immune checkpoint inhibitors have also been observed. These characteristics suggest that this therapy may be effective for a wider range of cancer types. We hope that selective Treg removal will become a new therapeutic approach that enables complete cancer remission.

CCR8 is specifically expressed on tumor-infiltrating Tregs

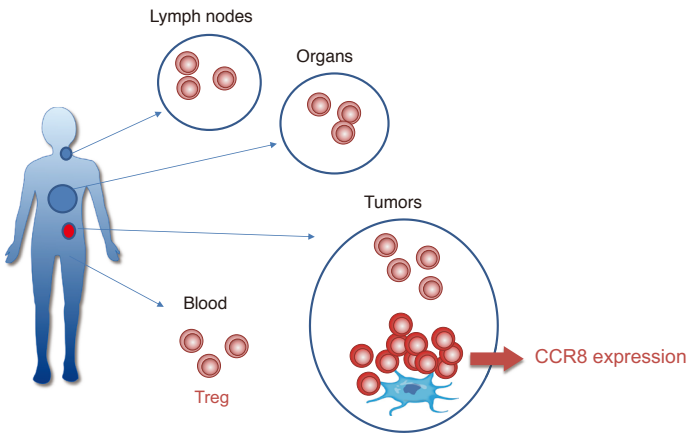


Fig 1

Anti-CCR8 antibody can induce anti-tumor immunity, while avoiding autoimmunity

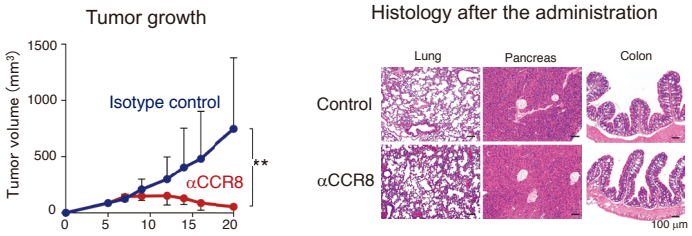
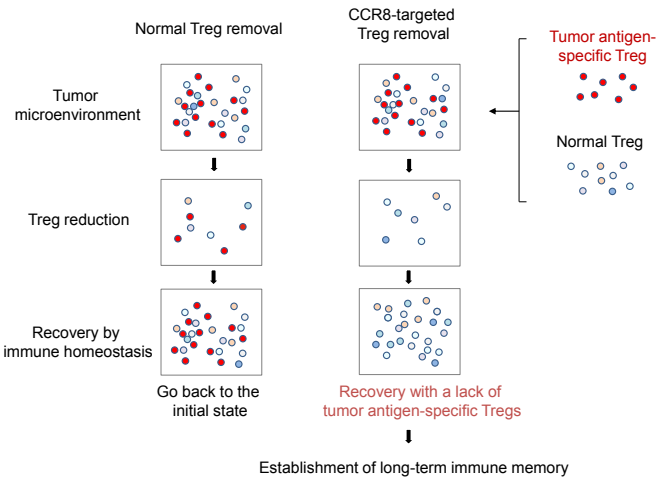


Fig 2

By selective removal of tumor antigen-specific Tregs long-term anti-tumor immune memory is established



Supplementary Figure

Patent JP6501171, US10550191, CN110573180, AU2018243020, KR10-2144658, RU2730984, JP6894086, RU2782462.

Treatise Kidani, Yujiro et al. CCR8-targeted specific depletion of clonally expanded Treg cells in tumor tissues evokes potent tumor immunity with long-lasting memory. Proc Natl Acad Sci U S A. 2022, 119(7), e2114282119. doi: 10.1073/pnas.2114282119

URL

Keyword regulatory T cells, CCR8, cancer immunotherapy, autoimmune disease