News Release

Title Optimization of Chimeric Antigen Receptor (CAR) Structure Enables Fine-Tuning of Signaling and Successful Creation of Clinically Usable CD37 CAR-T Cells

Key Points

- The activation signal of CD37CAR-T cells could be fine-tuned by changing the structure of CD37CAR-T cells.
- When the length of the extracellular portion was long, CD37CAR-T cells recognized their own CD37 antigen and killed each other (fratricide), but by shortening the extracellular portion, they did not kill each other.
- By shortening the extracellular portion and preventing fratricide, we were able to create CD37CAR-T cells that can be used in clinical applications.

Summary

A research group led by Professor Hitoshi Kiyoi of the Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Lecturer Seitaro Terakura of the Department of Hematology, Nagoya University Hospital, and graduate students Shingo Okuno and Yoshitaka Adachi has successfully generated novel chimeric antigen receptor (CAR) transduced T-cells (CAR-T) against the CD37 antigen expressed in B-cell malignant lymphoma (CD37CAR-T cells).

CAR-T cell therapy against CD19 antigen, which has been introduced as a new treatment for relapsed and refractory malignant lymphoma in recent years, shows remarkable therapeutic effects against CD19-positive malignant lymphoma, but on the other hand, it is known that CD19-negative lymphoma may recur after treatment (CD19-negative relapse). Thus, it was thought that a countermeasure was necessary. Therefore, the research group selected CD37 as a new target antigen and developed a CAR-T against CD37. In the process, the research group found that modifying the CAR structure changes the signal strength transmitted after binding to the CD37 target. By using this alteration, they were able to create clinically usable CD37 CAR-T cells. In the case of the CD37 antibody used by the research group, the long-version of the connecting domain between the antigen recognition site and the CAR-T cells causes strong signals to be transmitted, which leads to the recognition of self-antigens and kills each other (fratricide), whereas the short-version of the connecting domain between the antigen recognition site and the cells regulates the signals transmitted and prevents fratricide. Thus, by shortening the connecting domain between the antigen recognition site and the cell, we were able to modulate the signal transmitted and prevent the cell from fighting each other. This finding will be useful for the development of CARs against various target antigens other than CD37, in order to obtain the optimal structure for each target antigen.

The results of this research were published in the international scientific journal "The Journal of Immunology" (electronic version dated June 07, 2021).

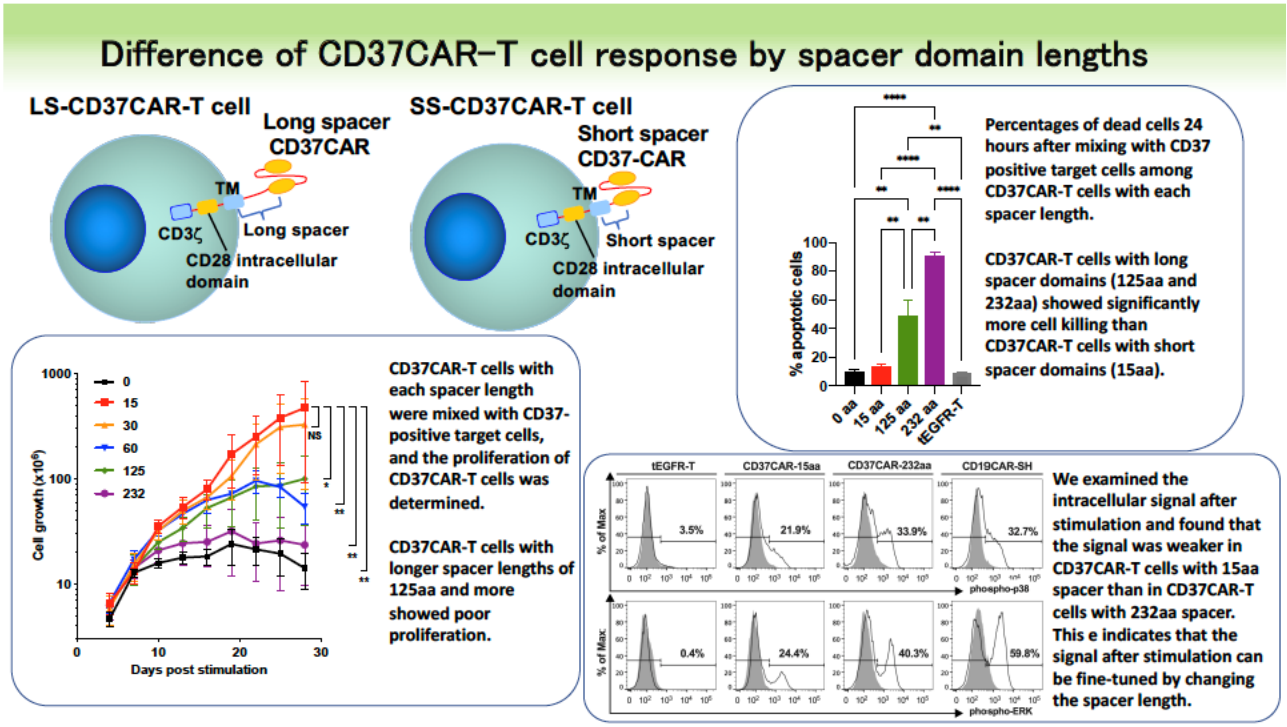
Research Background

Treatment with CAR-T cells against CD19 antigen, which was recently introduced as a novel therapy for relapsed and refractory (R/R) malignant lymphoma, has shown tremendous therapeutic efficacy against CD19-positive malignant lymphoma. On the other hand, it is known that the tumor may recur as CD19-negative upon relapse after treatment (CD19 negative relapse), and it was thought that countermeasures against CD19-negative relapse were necessary. Dual CAR-T cells that target two antigens simultaneously, such as CD22 in addition to CD19 are being developed for R/R acute lymphocytic leukemia. To target a new target antigen simultaneously with CD19, we have developed CAR-T cells against CD37, which is frequently expressed on the surface of malignant lymphoma cells.

Research Results

We generated CD37CAR-T cells by modifying antibodies against CD37, and generated several types of CD37CAR-T cells with long and short extracellular spacer domains connected to the CD37 antibody portion that binds to CD37. CAR-T cells with a long spacer (long-spacer, LS) recognized the weakly expressed CD37 on theirselves, and CD37CAR-T cells with LS killed each other (fratricide). In contrast, when the spacer domain was shortened (short-spacer, SS), there was almost no killing observed, and the intracellular signal after CD37 stimulation was found to be weaker in SS-CD37CAR-T cells. By adjusting the length of the spacer domain, the signal transmitted into the cells could be fine-tuned.

The CD37 CAR-T cells generated in this way recognized CD37 on the tumor cell surface and showed excellent CAR-T proliferation after CD37 stimulation. On the other hand, the CD37CAR-T cells hardly responded to the very weakly expressed autologous CD37. In other words, it was assumed that the administration of the generated CD37 CAR-T cells into humans would not cause any major adverse reactions. When CD19CAR-T cells and CD37CAR-T cells were administered to immunodeficient mice inoculated with tumor cell lines, some of the mice in the CD37CAR-T cell group were cleared of tumors, and the CD19CAR-T cell group had a significantly better therapeutic effect. This was explained by the attenuated intracellular signal after stimulation in SS-CD37CAR-T cells.



Research Summary and Future Perspective

We have developed a CD37 CAR-T cell that can be administered clinically. In addition to CD19, CD37 can be used as a target antigen for CAR-T cell therapy of lymphoma. Currently, our group is developing Dual CAR-T cells to target both CD19 and CD37 antigens simultaneously. Our goal is to develop clinically applicable CD19/CD37 dual CAR-T cells.

Publication

“Spacer length modification facilitates discrimination between normal and neoplastic cells and provides clinically relevant CD37 CAR-T cells”

The Journal of Immunology (electronic version dated June 07, 2021)
DOI：https://doi.org/10.4049/jimmunol.2000768

Japanese ver.:
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/jou_imm_210607.pdf