Press Release

Keio University

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Keio University School of Medicine

Team Rejuvenates Exhausted T Cells to Successfully Produce T Cells with Strong Anti-tumor Effects

Development of a Novel CAR-T Cell Therapy for Cancer Immunotherapy

A research team led by Professor Akihiko Yoshimura of the Department of Microbiology and Immunology at the Keio University School of Medicine has developed a simple method to rejuvenate exhausted T cells and induce T cells with strong anti-tumor effects, suitable for CAR (chimeric antigen receptor) -T cell therapy.

CAR-T cell therapy is a cancer treatment in which T cells derived from the peripheral blood of cancer patients are transferred back to the patients after introducing CAR, a gene that recognizes cancer cells. While T-cell therapies, including CAR-T cell therapy, have been attracting attention as effective cancer treatments, ex vivo expansion of T cells results in the "exhaustion" of T-cells, which reduces their anti-tumor effects. Therefore, various efforts have been made to "rejuvenate" exhausted T cells into young memory T cells, also known as stem cell-like memory T cells or T_{SCM}. T_{SCM} cells can actively divide and produce many daughter cells that can attack cancer. The method to convert exhausted T cells into T_{SCM} cells, however, has not yet been established.

The research team successfully converted exhausted T cells into T_{SCM} cells by culturing the CAR-T cells in the presence of a combination of four factors, namely IL-7, CXCL12, IGF-I, and NOTCH ligand, and named these cells CAR-iT_{SCM} cells. CAR-iT_{SCM} cells proliferate quickly in response to cancer cells, have a long lifespan, and exhibit stronger anti-tumor effects than conventional CAR-T cells.

The results of this research were recently published in *Cancer Research Communications*, a journal of the American Cancer Society.

1. Research Background

Immune cells, especially T cells, are extremely important for eliminating viruses, bacteria, and cancer cells from the body, and recently, CAR-T cell therapy has emerged as an efficient cancer immunotherapy. CAR (chimeric antigen receptor) is an artificial gene that can recognize cancer cells and produce signals for the proliferation and activation of T cells. In CAR-T cell therapy, peripheral blood T cells that have been isolated from patients are genetically modified to express the CAR gene. The resulting CAR-T cells are expanded in vitro until a sufficient number of CAT-T cells are obtained for therapy, then returned to the cancer patient (See Fig. 1).

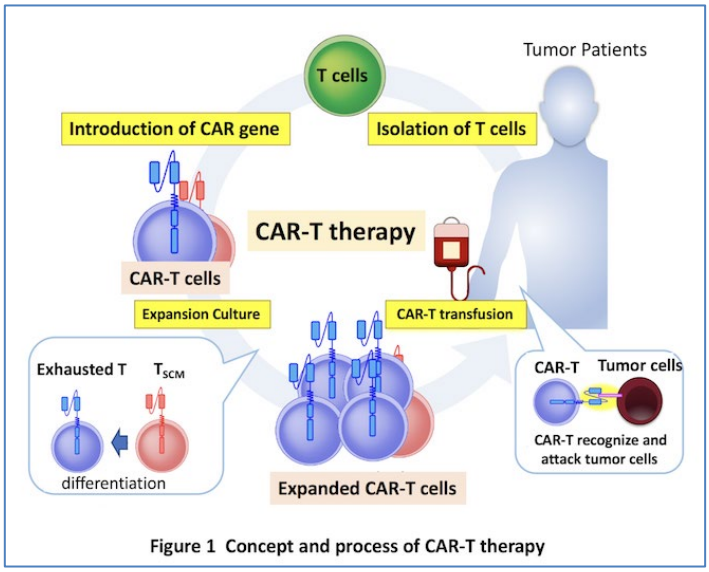


Figure 1 Concept and process of CAR-T therapy

However, when T cells are repeatedly stimulated in the body or in vitro, they fall into a state of "exhaustion" in which T cells are less proliferative and cannot kill tumor

cells. It has been shown that patients who are resistant to cancer immunotherapy have more exhausted T cells and fewer young memory T cells. Among various memory T cells, stem cell memory T (T_{SCM}) cells are the memory T cells that are closest to naïve T cells, are the longest-lived, and can produce a large number of daughter T cells that can effectively attack tumor cells. Therefore, it is vital to reduce exhausted T cells and produce more T_{SCM} cells for successful cancer immunotherapy (See Fig. 2). However, until now, there have been few methods for converting exhausted T cells into T_{SCM} cells.

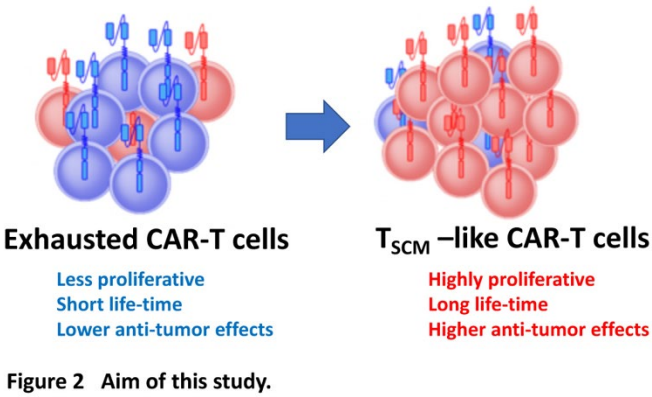


Figure 2 Aim of this study.
Rejuvenating Exhausted CAR-T Cells into Stem Cell Memory–Like CAR T (CAR-iTSCM) Cells

2. Results of the research

The research team has previously reported how CAR-T cells can be rejuvenated to T_{SCM}-like T cells by culturing them with a murine feeder cell line, OP9-hDLL1 cell. They named these cells "stem cell memory-like CAR-T cells (CAR-iT_{SCM})." However, this method uses mouse-derived cells, which are not suitable for clinical application. In this study, the research team aimed to establish a feeder-free culture system to rejuvenate exhausted CAR-T cells into iT_{SCM} cells by defining the factors that can support such rejuvenation. As a result of screening for factors expressed by feeder cells, the team discovered four factors: IL-7, IGF-I, CXCL12, and NOTCH ligand for sufficient induction of CAR-iT_{SCM} cells (See Fig. 3).

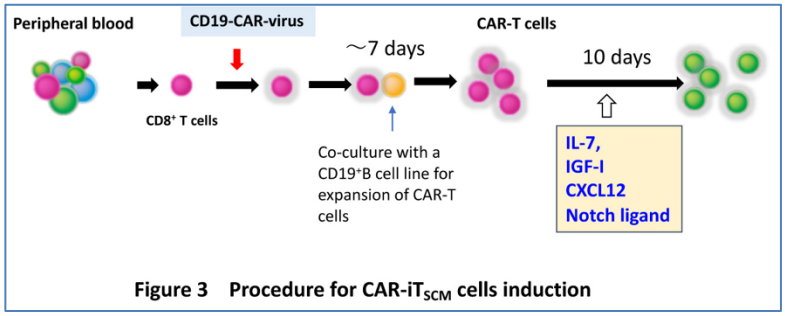
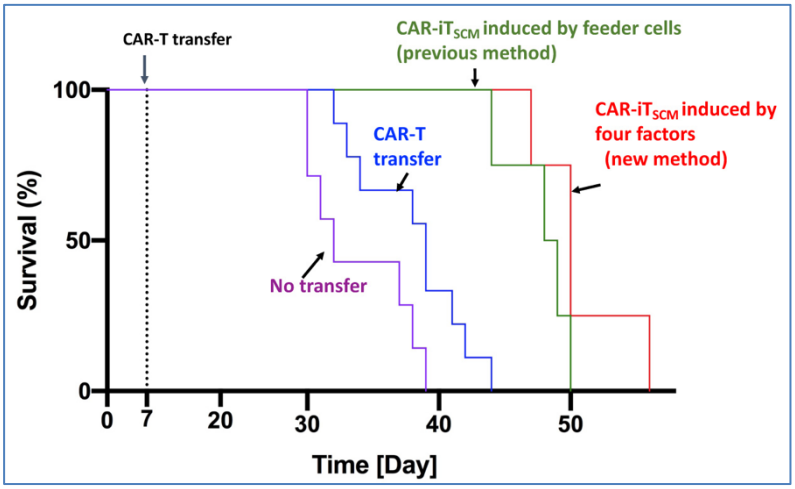


Figure 3 Procedure for CAR-iT_{SCM} cells induction

Obtained CAR-iT_{SCM} cells exhibited early memory phenotypes and showed longer lifetime and higher antitumor effects than conventional CAR-T cells (See Fig. 4).



3. Future Prospects

The culture system developed in this study enabled the rejuvenation of exhausted CAR-T cells into stem cell memory-like CAR-T cells with stronger anti-tumor effects. Since this method is simple and uses only defined protein factors, it is expected to be clinically applicable in the near future.

At present, CAR-T cell therapy is only effective for hematological cancers, as solid tumors are considered to be difficult to treat with CAR-T cell therapy. The CAR-iT_{SCM} cells developed by this new method are expected to have therapeutic potential on solid tumors. Clarification of the molecular mechanism of CAR-iT_{SCM} induction will lead to the development of new drugs which convert exhausted T cells into T_{SCM} cells within the body of cancer patients.

4. Notes

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5. Research Paper

Title：Rejuvenating effector/exhausted CAR-T cells to stem cell memory-like CAR-T cells by resting them in the presence of CXCL12 and the NOTCH ligand

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