News Release

Discovery of a New Mechanism Supporting the Efficacy of CAR-T Cancer Immunotherapy: Cholesterol Biosynthesis Identified as a Key Driver of Long-Term CAR-T Cell Activity

Key Points

- We identified part of the mechanism underlying the long-term persistence of CAR-T cell therapy.
- We discovered that the metabolic pathway responsible for producing cholesterol plays a crucial role in maintaining CAR-T cell function.
- Through both patient data analyses and cellular experiments, we demonstrated that this metabolic pathway is associated with the persistence of CAR-T cells.
- These findings may contribute to the development of new therapeutic strategies to further enhance the efficacy of CAR-T cell therapy.

Summary

A research group led by graduate student Yuki Takeuchi, Assistant Professor Ryo Hanajiri, Lecturer Seitaro Terakura, and Professor Hitoshi Kiyoi from the Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, has identified a new mechanism that enables CAR-T cells used in cancer immunotherapy to achieve long-term persistence in the body.

CAR-T cell therapy is a treatment in which a patient's own immune cells (T cells) are genetically modified outside the body to recognize and efficiently attack cancer cells, and then infused back into the patient. This therapy has demonstrated remarkable clinical efficacy, particularly in certain hematologic malignancies. However, the duration for which CAR-T cells persist and remain functional after infusion varies among patients, and these differences are believed to influence long-term treatment outcomes. Until now, the precise biological mechanisms that determine the persistence of CAR-T cells have not been fully understood.

In this study, the researchers performed comprehensive analyses of gene expression and protein changes in CAR-T cells, combined with cellular experiments and analyses of patient data. They found that the metabolic pathway responsible for cholesterol production (cholesterol biosynthesis) plays a critical role in sustaining CAR-T cell function. Although cholesterol is

commonly associated with metabolic diseases, it is also an essential component of cell membranes and plays important roles in cell growth and functional maintenance. The study demonstrated that CAR-T cells with higher activity of cholesterol biosynthesis pathways exhibited enhanced proliferative capacity and were more likely to persist longer in the body. Furthermore, experimental modulation of this metabolic pathway using pharmacologic agents altered CAR-T cell proliferation and function, providing direct evidence that cholesterol metabolism is an important regulator of CAR-T cell activity.

These findings suggest that optimizing the metabolic state of CAR-T cells could represent a novel therapeutic strategy to enhance the durability of CAR-T cell therapy. The results are expected to contribute to the development of next-generation CAR-T therapies with improved long-term efficacy, as well as new biomarkers that may help predict treatment responses and guide personalized therapeutic strategies.

These findings were published in the Journal for ImmunoTherapy of Cancer, a journal of the Society for Immunotherapy of Cancer, on March 12, 2026.

Research Background

CAR-T cell therapy is a novel treatment approach in which a patient's own immune cells are genetically modified to recognize and attack cancer cells. This therapy has demonstrated remarkable clinical efficacy, particularly in certain hematologic malignancies that were previously difficult to treat. However, long-term treatment benefits are not achieved in all patients. Clinical outcomes and the risk of relapse are strongly influenced by how long CAR-T cells persist and remain functional in the body after infusion. Therefore, understanding the biological mechanisms that enhance CAR-T cell persistence and developing strategies to prolong therapeutic efficacy have become major research priorities. In addition, the ability to predict, before treatment, which patients are more likely to achieve durable CAR-T cell persistence could help guide more appropriate treatment selection. For these reasons, there has been a strong need to elucidate the molecular mechanisms that support the long-term survival and functional maintenance of CAR-T cells in vivo.

Research Results

To elucidate the mechanisms that enable CAR-T cells to remain functional over long periods in the body, we conducted an integrated analysis combining gene expression profiling, proteomic analyses, functional cellular assays, and patient

data evaluation. Our results demonstrated that CAR-T cells exhibiting higher activity of the metabolic pathway responsible for cholesterol production (cholesterol biosynthesis) showed enhanced proliferative capacity, maintained functional activity, and tended to persist longer. Although cholesterol is widely recognized for its association with metabolic diseases, it is also an essential structural component of cellular membranes and plays critical roles in cell growth and functional maintenance. These findings provide new evidence that cholesterol metabolism is closely linked to the persistence of CAR-T cells.

Further analyses revealed that CAR-T cells carrying specific CAR constructs displayed stronger activation of cholesterol biosynthesis–related genes and proteins. In addition, cellular experiments using pharmacologic modulation of cholesterol synthesis showed that inhibition of this pathway resulted in reduced CAR-T cell proliferation and functional activity, experimentally confirming that cholesterol metabolism is an important factor supporting CAR-T cell function. Consistent with these laboratory findings, analyses of clinical patient data also identified associations between circulating lipid-related parameters and the persistence of CAR-T cells in vivo, demonstrating concordance between experimental and clinical observations.

When different types of CAR-T cells were compared, CD28-based CAR-T cells showed relatively lower cholesterol biosynthetic activity and tended to exhibit more limited proliferation and persistence in vivo. In contrast, CAR-T cells incorporating 4-1BB or CD79a/CD40 signaling domains demonstrated more active cholesterol metabolism, enhanced proliferative capacity, and prolonged persistence in the body. These findings suggest that differences in CAR design can shape the metabolic characteristics of CAR-T cells, which may ultimately influence the durability of therapeutic responses.

Collectively, these findings suggest that appropriate regulation of the metabolic state of CAR-T cells may enhance their functional durability and persistence. The results provide important insights for the design of next-generation CAR-T constructs and the optimization of therapeutic strategies. Furthermore, the identification of metabolic characteristics as potential biomarkers may contribute to improved prediction of treatment outcomes and the development of personalized therapeutic approaches tailored to individual patients.

Research Summary and Future Perspective

This study suggests that metabolic pathways centered on cholesterol biosynthesis play an important role in the persistence and functional maintenance of CAR-T cells. Future research will focus on more detailed analyses of the metabolic states of CAR-T cells to determine the conditions under which this pathway most effectively supports cellular function, ultimately contributing to the design of CAR-T cells capable of maintaining strong antitumor activity over extended periods. In addition, molecules associated with cholesterol metabolism may serve as potential biomarkers for predicting the durability of CAR-T cell responses before treatment, and the development of new therapeutic strategies combining CAR-T therapy with metabolic modulators represents another important direction for investigation. Furthermore, applying these findings to other cancer types and various immune cell–based therapies may help improve the overall effectiveness of cancer immunotherapy. Ongoing efforts integrating both basic and clinical research will be essential to translate these discoveries into practical clinical applications.

Publication

Journal for ImmunoTherapy of Cancer

CD79A/CD40 Intracellular Domain Utilizes a 4-1BB-Like Metabolic Pathway Driven by Cholesterol Biosynthesis

Yuki Takeuchi[1], Seitaro Terakura[1], Kohei Ishigiwa[1], Jakrawadee Julamanee[1,2], Shiho Hirano[1], Hirofumi Yokota[1], Shihomi Kuwano[1], Ryo Hanajiri[1], and Hitoshi Kiyoi[1]

[1]Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[2]Stem Cell Laboratory, Hematology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

DOI: 10.1136/jitc-2025-012309

Japanese ver.

https://www.med.nagoya-u.ac.jp/medical J/research/pdf/Jou 260312.pdf