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○ 受賞の感想と今後の抱負

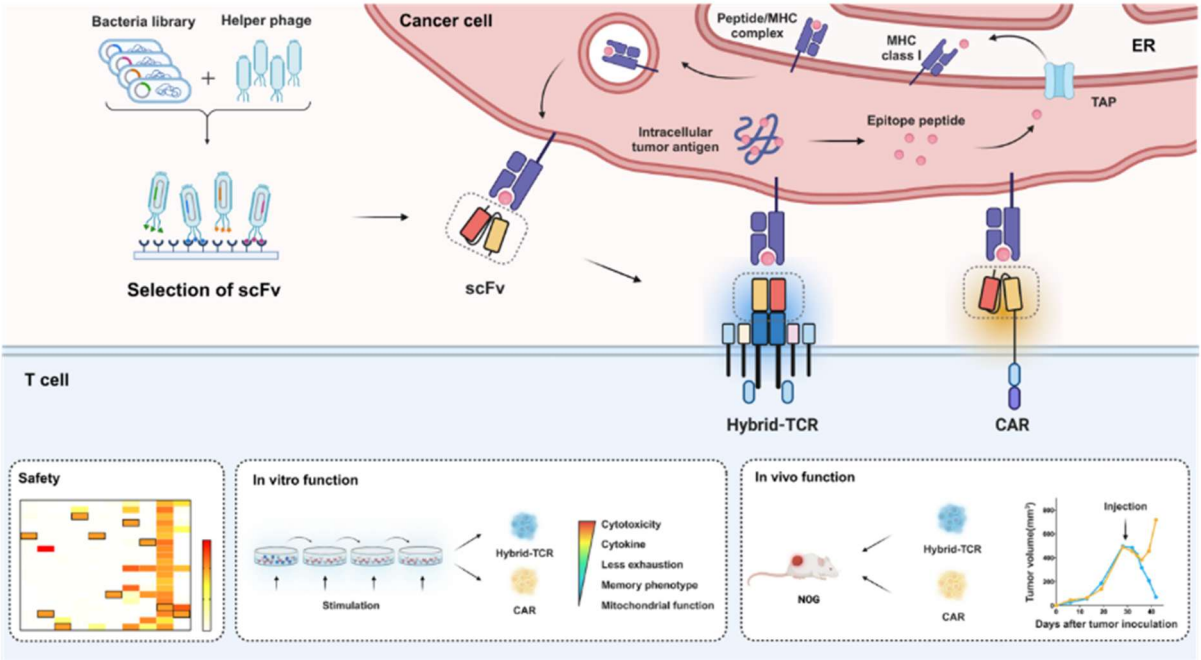
この度は、三重医学若手研究者賞という名誉ある賞を賜り、誠に光栄に存じます。本学医学系研究科個別化がん免疫治療学の宮原慶裕教授をはじめ、日頃よりご指導とご支援を賜りました諸先生方ならびに関係各位に、心より感謝申し上げます。本受賞を励みとし、これまでに培った知見と経験を今後の研究活動に活かし、学術の発展および医学への貢献を目指して、引き続き誠実に研鑽を重ねてまいります。

○ 受賞テーマ

「Exploring GITR Co-Stimulation to enhance the functions in pMHC (peptide/MHC complex) targeted CARs」

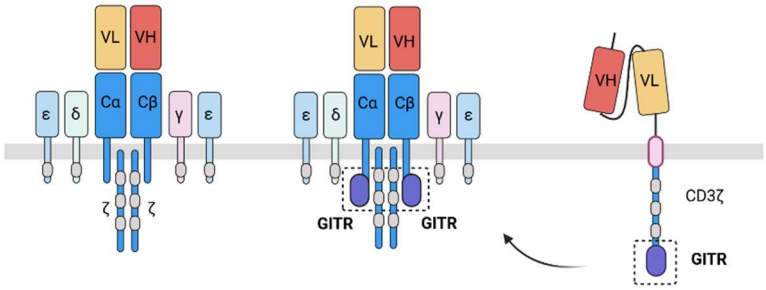
○ 研究の概要と将来展望

The lack of suitable target antigens is one of the primary limitation of Chimeric Antigen Receptor (CAR)-T cell therapy for solid tumors. Targeting intracellular antigens through peptide MHC complex (pMHC) can be a promising strategy to overcome this challenge in CAR-T cell therapy. In the previous study, we developed the peptide/MHC-specific CAR-T cells that enable CAR-T cells to recognize intracellular tumor-specific antigens. Nonetheless, further exploration of more functional CAR structures is still demanded.

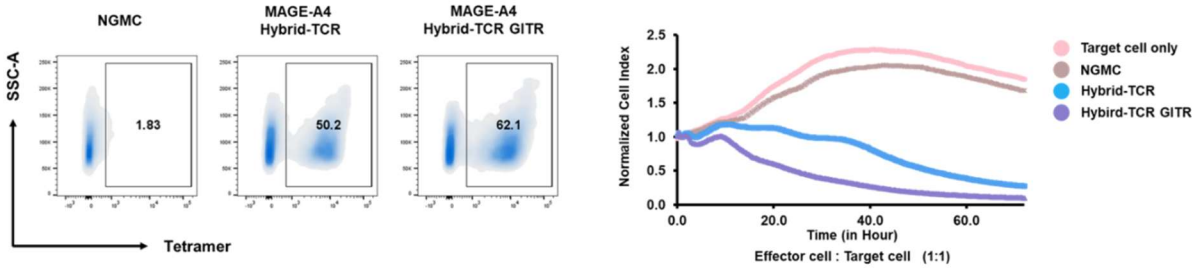


In addition, we designed a novel CAR (Hybrid-TCR) in which constant regions of TCR beta and alpha fused with VH and VL domains of the scFv antibody, respectively. Compared to traditional CAR-T cells, MAGE-A4 Hybrid-TCR T cells significantly enhance the antitumor effects in vitro and in vivo while retaining the same stringent specificity as MAGE-A4 CAR T cells.

To further enhance function of Hybrid-TCR T cells, we consider incorporating co-stimulatory molecular to improve its efficacy. Based on previous studies where glucocorticoid-induced tumor necrosis factor receptor (GITR) co-stimulation shows stronger in vivo anti-tumor effects in pMHC targeting CAR-T cells, we incorporated a GITR domain into T cells to provide autonomous co-stimulation.



We constructed the vectors and transfected them into PBMCs. Those Hybrid-TCR T cell could be recognized by tetramer staining, and we also observe that, in long term cytotoxicity analysis Hybrid-TCR with GITR co-stimulation group shows better sustained cytotoxic capacity. In the future, we will conduct further experiments on their in vivo and in vitro functions.



○ 関連分野における本研究の特筆すべき点

Compared to traditional CAR-T cells, Hybrid-TCR T cells have significantly enhanced antitumor effects both in vitro and in vivo, while retaining the same specificity as CAR-T cells. Nevertheless, their functionality still has room for further improvement. One promising strategy is the integration of the GITR co-stimulatory pathway into Hybrid-TCR T cells. GITR signaling, known to promote effector T-cell proliferation, persistence, and the capacity to overcome inhibition imposed by regulatory T cells. These mechanisms could enhance the in vivo persistence of Hybrid-TCR T cells and resist immunosuppressive tumor microenvironment. The integration of GITR co-stimulation into Hybrid-TCR T cells has not yet been explored and could offer a possible approach to improve target pMHC immunotherapy and potentially leading to more effective treatments in the near future.

○ 本研究の将来期待される点

Integrating GITR co-stimulation into Hybrid-TCR T cells holds promise for enhancing the therapeutic potential of C Hybrid-TCR T cell therapies against solid tumors. In the next phase of research, we will conduct further in vivo and in vitro experiments to compare the functional changes resulting from Hybrid-TCR integration with GITR co-stimulation.

We will also perform deeper mechanistic analysis to research how GITR signaling pathway effector function within the immunosuppressive tumor microenvironment. In the future, we will further evaluate whether GITR co-stimulation Hybrid-TCR cells may can be combined with adjunctive therapies such as immune checkpoint blockade to achieve more durable antitumor responses. Collectively, these studies are expected to provide the foundation for next-generation Hybrid-TCR therapies designed to overcome current bottlenecks in solid tumor immunotherapy.

○ 本研究に関連する代表的な原書学術論文（1 編）

Meiou Liu, Yasushi Akahori, Naoko Imai, Linan Wang, Kohei Negishi, Takuma Kato, Hiroshi Fujiwara, Hiroshi Miwa, Hiroshi Shiku, Yoshihiro Miyahara, MAGE-A4 pMHC-targeted CAR-T cells exploiting TCR machinery exhibit significantly improved *in vivo* function while retaining antigen specificity, The Journal for ImmunoTherapy of Cancer, Volume 12, Issue 11, e010248, November, 2024

○ 略歴

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○ 専門分野

免疫学、腫瘍診断、治療学

○ 医学博士、専門医資格など

三重大学大学院医学系研究科 生命医科学専攻 医学博士