News Release

Title: Newly developed composite CD79A/CD40 costimulatory endodomain enhances CD19CAR-T cell proliferation and survival

Key Points

- An innovative composite costimulatory domain of a B-cell signaling moiety, CD79A/CD40, induced strong nuclear translocating signal, NF-κB, to synergize with T-cell signals and improve CAR-T cell function.
- CD19CAR incorporated CD79A/CD40 endodomain demonstrated robust CAR-T cell proliferation and improved anti-tumor efficacy in Raji (lymphoma)-inoculated mice.
- CD79A/CD40 endodomain may convey better survival than currently used CD28 or 4-1BB endodomain.

Summary

Graduate student Jakrawadee Julamanee (1st author), Lecturer Seitaro Terakura (Correspondence), and Professor Hitoshi Kiyoi of the Department of Hematology and Oncology, Nagoya University Graduate School of Medicine developed a composite costimulatory domain of a B-cell signaling moiety, CD79A/CD40, to induce a nuclear translocating signal, NF-κB, to synergize with T-cell signals and improve chimeric antigen receptor (CAR) T-cell function.

Recently, a gene modified to express CD19CAR-T cell unveiled promising outcomes in B-cell malignancies. Successful treatments seen in landmark clinical trials using second-generation CD19CAR-T cells incorporating either 4-1BB or CD28 costimulatory domains led the US Food and Drug Administration (FDA) approved CD19CAR-T cell for treating relapsed/refractory B-ALL and B-NHL patients. Despite the high initial response rates, relapses still occur in a significant number of patients that the poor CAR-T cell proliferation and long-term persistence in vivo are correlated with incomplete response and early relapse. To enhance CAR-T cell proliferation and persistence, the research group generated a novel third generation CD19CAR incorporated CD79A/CD40 signaling domain (CD19.79a.40z CAR) which induced strong T-cell signaling upon CD19 antigen stimulation. CD19.79a.40z CAR-T cells exhibited robust CAR-T cell proliferation and could suppress cancer cell growth both in vitro and in vivo B-cell lymphoma model. This group confirmed the possibility of incorporating B-cell signaling moiety into a CAR structure, which enhanced CAR-T cell proliferation and persistence. CD79A/CD40 endodomain may sustain the durable remission and ultimately improve outcomes in B-cell lymphoma. This work was published in the international scientific journal “Molecular Therapy”, electronic version on 1 May 2021.

Research Background

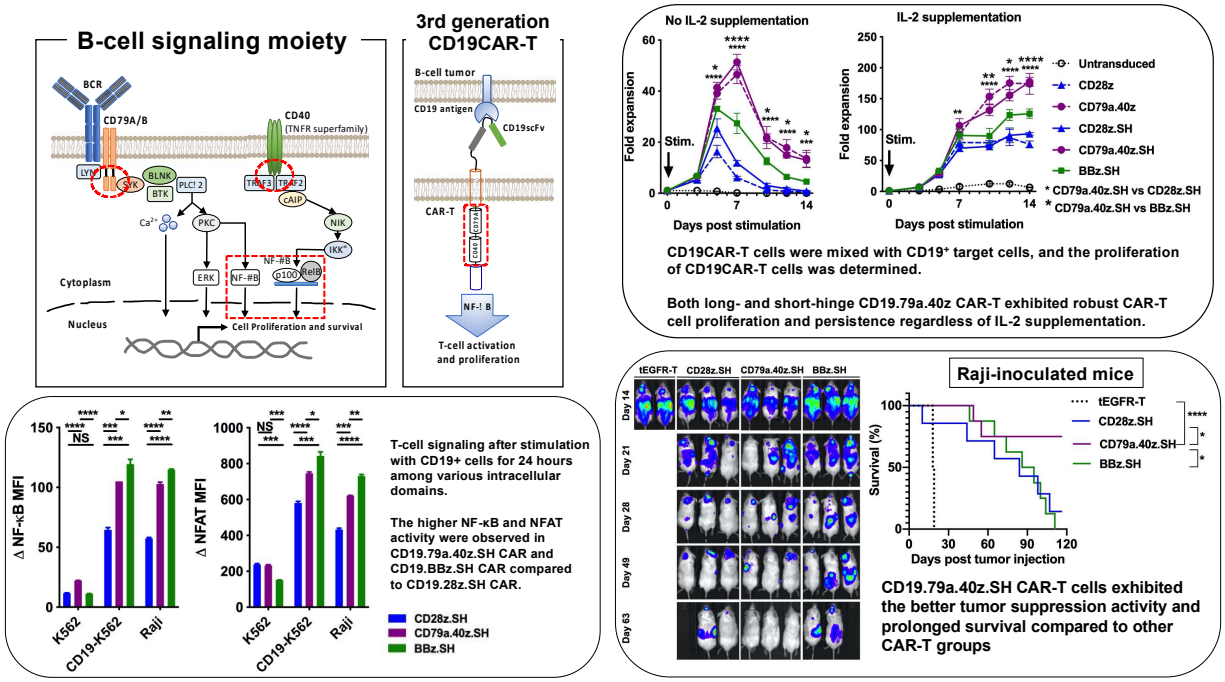
As the NF-κB was demonstrated as a crucial signaling pathway for 4-1BB costimulation and contributed to increase in CAR-T cell proliferation and persistence compared to CD28. The research group therefore attempted to increase NF-κB signaling in CAR-T cells by introducing the B-cell receptor (BCR) coreceptor, CD79A, and CD40 signaling domains to generate the third generation CD19CAR-T cell. They hypothesized that the CD79A/CD40 endodomain would cooperate to exert crucial intracellular signaling, mainly involving NF-κB, to synergize with T-cell signaling and improved CAR-T cell function.

Research Results

They developed an innovative CD19CAR incorporated the composite CD79A/CD40 costimulatory domain (CD19.79a.40z) with both long- and short-hinge version into original CD19CAR backbone and compared to the well-established CD28 and 4-1BB costimulatory domains. CD19.79a.40z CAR exhibited increased NF-κB and NFAT signaling upon CD19 stimulation. Notably, they observed the greater CAR-T cell expansion and maintained after 2 weeks of culture, regardless of cytokine supplementation. Owing to the prominent T-cell growth, CD19.79a.40z CAR-T cells continuously suppressed tumor cell growth in long-period of co-culture assay despite low effector to target cell ratios. Moreover, CD19.79a.40z CAR-T cells profoundly suppressed tumor cell growth in both NALM-6 or Raji-bearing mice, leading to long-term effective tumor clearance and prolonged overall survival compared to CD19.28z CAR-T and CD19.BBz CAR-T cells.

In this study, the enhancement of NF-κB and NFAT signaling by the CD79A/CD40 costimulatory domain attributed to the greater CAR-T cell proliferation and persistence. In addition, they observed the distinct kinetics of tumor eradication that CD19.79a.40z CAR-T cells showed a relatively slow-starting but long-lasting response which caused the more survival outcome in Raji-inoculated lymphoma model compared to that in NALM-6 leukemia model. On the other hand, mice treated with other conventional CD19CAR-T cells could not achieve complete tumor response due to the low CAR-T cell expansion, which led to early tumor recurrence and poor survival outcomes.

The composite B-cell signaling moiety, CD79A/CD40, enhances CD19CAR functions



Research Summary and Future Perspective

An innovative CD79A/CD40 costimulatory domain was developed, and demonstrated to enhance CD19CAR-T cell proliferation and persistence. CD19.79a.40z CAR-T cells possibly sustain the durable remission and prolong survival in B-cell lymphoma patients. CD79A/CD40 costimulatory domain is underway for patent application. Currently, the research group is optimizing the dual T/B-cell intracellular domains and clinically applicable CD19CAR-T cells.

Publication

Julamanee J, Terakura S, Umemura K, Adachi Y, Miyao K, Okuno S, Takagi E, Sakai T, Koyama D, Goto T, Hanajiri R, Hudecek M, Steinberger P, Leitner J, Nishida T, Murata M, Kiyoi H, Composite CD79A/CD40 costimulatory endodomain enhances CD19CAR-T cell proliferation and survival, Molecular Therapy (2021),

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