QUALITY IMPROVEMENT OF ANTI-CD38-JAK/STAT CAR-T CELLS BY SUPPRESSING CD38 EXPRESSION AND INHIBITION OF TYROSINE KINASE

Yasunori Amaishi*, Izumi Maki, Maiko Sugizaki, Kenichiro Mihara, Sachiko Okamoto, Junichi Mineno. Takara Bio Inc., Kusatsu, Shiga, Japan; Fujita Health University, Toyoake, Aichi, Japan

Background CAR-T cell therapy has shown highly effective clinical results in several diseases, but further improvement is necessary to target a wider range of antigens and tumors. In particular, excessive activation of CAR-T cells leads to cell exhaustion and reduction of naive/memory T cells population, which are important for long-term immune response. Therefore, suppressing non-antigen-specific activity is necessary for CAR-T cell production. However, when targeting tumor-related antigens that are also expressed on T cells, CAR-T cells recognize the antigens on the T cells, resulting in fratricide, poor cell growth, differentiation, and exhaustion during cell production process. In this study, we investigated a method for producing CAR-T cells targeting CD38 antigen that is common to T cells and tumor cells. CD38 is a suitable target antigen for CAR-T cell therapy because it is highly expressed in lymphocyte malignant tumors including B-cell non-Hodgkin’s lymphoma and multiple myeloma. However, as it is also intermediately expressed in normal blood cells, unwanted activation of CAR-T cells may be caused.

Methods We tried to suppress the expression of CD38 in CAR-T cells by co-expressing CD38 siRNAs, and prevent activation during cell production by modifying the signal domain of anti-CD38-CAR to the newly developed JAK/STAT-CAR. JAK/STAT-CAR contains the intracellular domain of the IL-2 receptor β chain and the STAT3 binding motif, which have been shown to improve the proliferation of CAR-T cells and suppress differentiation compared to conventional second-generation CAR-T cells. For further improvement, CAR-T cells were prepared in the presence of the tyrosine kinase inhibitor Dasatinib to suppress activation during the cell manufacturing process.

Results CD38 siRNA co-expressing CAR-T cells showed decreased expression of CD38 and exhaustion markers, and the further reduction of exhaustion marker expression was observed in JAK/STAT CAR-T cells. However, compared to CAR-T cells targeting other antigens, CD38-CAR-T cells tended to be more exhausted and differentiated. As Dasatinib treatment maintained a high proportion of naive/memory T cells and was able to suppress exhaustion, combination of these approaches (CD38 siRNA-expressing CD38-JAK/STAT CAR-T cells with Dasatinib treatment) showed long-term persistence of antitumor activity in in vitro re-challenge assay.

Conclusions CD38 siRNA co-expressing CD38-JAK/STAT CAR-T cells produced in the presence of a tyrosine kinase inhibitor are expected to be suppressed excessive activation and maintain long-term antigen-specific activity. This approach is also expected to be applied to other CAR-T cell therapies targeting tumor-related antigens expressed on T cells.

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