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Selective killing of malignant B cells using T cells redirected against malignancy variant receptor

Chungyong Han[1*], Sujung Sim[1], Kwang Hui Kim[1], Don Gil Lee[1], Ho Sik Oh[1], Sang Hyun Park[1], Sunhee Hwang[1], Won Young Kim[1], Sangeun Lee[1], Young Ho Kim[1], Beom Kyu Choi[1], Carl June[2], Byoung Se Kwon[1]

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Background

Advances in gene-transfer system and in-depth understanding of immune mechanism have made the immunotherapy a powerful tool for fighting against cancers. Recent studies demonstrated a therapeutic potential of T cells with chimeric antigen receptor (CAR) targeting CD19 in refractory hematopoietic malignancies. At the same time, however, hence the CD19 targeting results in normal cell destruction such as B cell aplasia, a novel marker that specifically expressed in malignant B cells should be applied. In this study, we developed anti-malignancy variant receptor (MVR) mAb that exclusively bound to malignant B cells but not to normal B cells, and demonstrated that autologous T cells expressing CAR construct with anti-MVR scFv (MVR-CAR T cells) efficiently suppressed the outgrowth of malignant B cells in lymphoid organs.

Results

Malignant B cell-specific monoclonal antibody was isolated from the Balb/c mice immunized with Burkitt's lymphoma cell line, L3055. The antibody specifically recognized the established B lymphoma cell lines and malignant B cells derived from acute lymphoblastic leukemia, chronic lymphocytic leukemia, and diffuse large B cell lymphoma patients. Q-TOF analysis revealed that anti-MVR mAb recognized one of the CD74 variants that distinctively expressed in malignant B cells. We used anti-MVR mAb to generate CAR T cells for the rapid and efficient production of autologous T cells targeting malignant B cells. MVR-CAR T cells were generated by stimulating T cells with anti-CD2, CD3, CD28 Ab-coated beads and transducing MVR-CAR construct using lentiviral vector system. Autologous MVR-CAR T cells efficiently induced cytotoxicity against EBV-transformed LCLs but not against the normal $CD19^+$ B cells *in vitro*. Furthermore, when the MVR-CAR T cells were adoptively transferred into immune-deficient $RAG2^{-/-}\gamma c^{-/-}$ mice into which LCLs were subcutaneously injected 3 weeks previously, they efficiently suppressed the outgrowth of metastasized LCLs in secondary lymphoid organs *in vivo*.

Conclusions

We developed anti-MVR mAb - a novel malignant B cell-specific antibody. Anti-MVR mAb recognized one of CD74 variants that exclusively expressed on malignant B cells. MVR-CAR T cells successfully induced LCL-specific cytotoxicity *in vitro* and *in vivo*. Considering the unique specificity on malignant B cells, anti-MVR mAb can be a therapeutic of B cell malignancies without normal B cell destruction.

Authors' details
[1]National Cancer Center, Gyeonggi-do, Republic Of Korea. [2]University of Pennsylvania, Philadelphia, PA, USA.

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[1]National Cancer Center, Gyeonggi-do, Republic Of Korea
Full list of author information is available at the end of the article