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703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

Targeting B-Cell Malignancies with Anti-ROR1 CAR T-Cell Therapy

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Anti-CD19 chimeric antigen receptor (CAR) T cell therapy has been shown to induce high complete response rates in the majority of B-cell lymphoma patients. However, over 50% of patients relapse within one year. A major cause of failure appears to be due to loss of CD19 expression on the tumor cell surface. This indicates that novel therapeutic strategies are still needed in clinic. Receptor tyrosine kinase like orphan receptor 1(ROR1) is an oncofetal receptor for Wnt5α that is expressed in multiple embryotic tissues but absent in virtually all adult tissues. However, ROR1 is expressed at high levels in chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), diffuse Large B-Cell Lymphoma (DLBCL), and several solid tumors. The high expression level of ROR1 in tumor cells is associated with adverse clinical prognosis. In addition, a small percentage of cancer cells with characteristics of undifferentiated leukemia cells or cancer stem cells were found to overexpress ROR1. Using hybridoma technology, we generated an anti-ROR1 monoclonal antibody that specifically recognized ROR1 protein. The antibody bound to ROR1-expressing MCL cell lines but not to normal donor T cells, B cells, or monocytes, indicating the specificity of the antibody. Lentiviral transduction of a CAR molecule derived from the anti-ROR1 antibody into primary human T cells redirected their specificity against B-cell lymphoma cell lines. We found the anti-ROR1 CAR T cells specifically lysed B-cell lymphoma tumor cells at high efficiency but not normal B cells. At an effector: target ratio of 1:1, the anti-ROR1 CAR T cells lysed over 95% of B-cell lymphoma tumor cells during 3-days of coculture. To determine the optimal CAR construct, we evaluated various hinge transmembrane, and costimulatory domains in the CAR molecule. We found that incorporation of the CD28 hinge and transmembrane domain in the CAR construct dramatically enhanced the in vitro lysis efficiency of anti-ROR1 CAR-T cells. In conclusion, we developed a novel and potent anti-ROR1 CAR T-cell therapy product that may be used for treatment of various B-cell malignancies and ROR1-expressing solid tumors.

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