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Genetically Engineered CLDN18.2 CAR-T Cells Expressing Synthetic PD1/CD28 Fusion Receptors and Signaling Mechanism Regulation Factor Produced Using a Lentiviral Vector

Abstract: This study aimed to develop synthetic Claudin18.2 (CLDN18.2) chimeric antigen receptor (CAR)-T (CAR-T) cells as a treatment for advanced gastric cancer using lentiviral vector genetic engineering technology that targets the CLDN18.2 antigen and simultaneously overcomes the immunosuppressive environment caused by programmed cell death protein 1 (PD-1). Synthetic CAR T cells are a promising approach in cancer immunotherapy but face many challenges in solid tumors. One of the major problems is immunosuppression caused by PD-1. CLDN18.2, a gastric-specific membrane protein, is considered a potential therapeutic target for gastric and other cancers. In our study, CLDN18.2 CAR was a second generation CAR with inducible T-cell costimulatory (CD278), and CLDN18.2-PD1/CD28 CAR was a third-generation CAR, wherein the synthetic PD1/CD28 chimeric-switch receptor (CSR) was added to the second-generation CAR. In vitro, we detected the secretion levels of different cytokines and the killing ability of CAR-T cells. We found that the secretion of cytokines such as interferon-gamma (IFN γ) and tumor necrosis factor-alpha (TNF-α) secreted by three types of CAR-T cells was increased, and the killing ability against CLDN18.2-positive GC cells was enhanced. In vivo, we established a xenograft GC model and observed the antitumor effects and off-target toxicity of CAR-T cells. These results support that synthetic anti-CLDN18.2 CAR-T cells have antitumor effect and anti-CLDN18.2- PD1/CD28 CAR could provide a promising design strategy to improve the efficacy of CAR-T cells in advanced gastric cancer. Recently, CARBio-022 CAR-T cells have added the X domain gene, which is a signaling mechanism regulation factor. The fifth generation CAR-T cells do not become exhausted, have excellent long-term and cancer-killing effects, but have the same body weight and are not toxic. Based on the 5th generation CARBio-022 CAR-T cells, we plan to prepare clinical trials targeting advanced gastric and pancreatic cancer using Mncl2. And we are rapidly developing treatments using organoids derived from patients with lung, liver, or biliary cancer.

Background: About 2,000 clinical trials are underway for CAR-T gene therapy, and the United States was the first in the world to conduct clinical trials in 1990, and clinical results have been announced in earnest since 2006. The long-standing dream of curing incurable diseases is gradually being realized, starting with the cure for blood cancer using CAR-T (Chimeric Antigen Receptor-T) gene therapy. It is a cutting-edge new medicinal technology that corrects, prevents, or treats diseases by synthesizing therapeutic genes and introducing them into the human body using a virus as a carrier.

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