Journal of Cancer Research and Immuno-Oncology

Liu, J Immunooncol 2016, 2:1

Editorial Open Access

Comment on the Current CAR-T Technology

Xiaowei Liu*

Center for Infectious Disease and Vaccinology, The Biodesign Institute, Arizona State University, USA

CAR T-cell refers to T cells engineered with the chimeric antigen receptor (CAR) technology, [1-3] which is a hottest topic of immunooncology. The CARs contain an extracellular single chain variable fragment (scFv) that recognizes and binds the target protein on cancer cells, an intracellular signaling (and costimulatory) domain that sends the activation signal to the cell and a transmembrane domain connecting the extracellular and intracellular domains. Depending on the number of costimulatory domains in each CAR, three generations of CAR have been developed [2]. Recognition and binding to the target protein brings and retains the CAR T-cells in close proximity to the cancer cell, which subsequently triggers T cells activation for cancer cell killing.

In T cell medicated immune responses, T cells recognize tumor antigens that are processed into fragments of peptides and presented with major histocompatibility complex (MHC), and tumor cells can down regulate expression of MHC to avoid recognition by T cells [4,5]. CAR T-cells, on the other hand, recognize intact tumor antigen through the extracellular scFv region, which does not rely on MHC, and therefore can circumvent the above mechanism. Moreover, given the variety of targets recognized by scFv, it is possible for CARs to recognize tumor antigens such as those of carbohydrate origin, thereby expanding its scope of treatment [5].

One of the major side effects or risk of CAR-T therapy is cytokine storm, which is the release of high levels of proinflammatory cytokines lead by extensive activation of CAR-T cells infused into patients [6]. To reduce such syndrome, investigators are working on different strategies such as introducing inhibitory switches that can down regulate T cell activation.

There are many biotech and pharma companies racing to get CAR-T into clinical use. Since the first clinical report by Novartis in 2011 [7], there are companies such as Novartis, Juno Therapeutics and Kite Pharma leading this race. Recently, FDA halted a phase 2 study of CD19-targeted CAR-T cell therapy JCAR015 by Juno therapeutics in adults with relapsed or refractory B-cell acute lymphoblastic leukemia, due to three deaths in this trial from cerebral edema. Although this hold was removed by FDA after less than a week, it did raised concerns on safety of CAR-T therapy. In Juno's new protocol design that was approved by FDA, pre-treatment of chemotherapy drugs were changed to cyclophosphamide alone, in contrast to the cocktail of fludarabine and cycslophosphamide in the previous protocol. As a purine analog, fludarabine is commonly used as a chemotherapy drug. There was report that pathological examination in patient receiving standard dose of fludarabine (25 mg/m^2/day for 5 days) showed cerebral edema [8].

The clinical trial of CAR-T is only about 5 years. It is still too early to draw a conclusion whether it can completely cure the cancer. But it is unquestionable there is early success. With more and more study spent on it, as well as more improvement made to this technology, we should look forward to better news for CAR-T.

References

1. Gross G, Waks T, Eshhar Z (1989) Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci 86: 10024-10028.
2. Gross G, Eshhar Z (2016) Therapeutic Potential of T Cell Chimeric Antigen Receptors (CARs) in Cancer Treatment: Counteracting Off-Tumor Toxicities for Safe CAR T Cell Therapy. Annu Rev Pharmacol Toxicol 56: 59-83.
3. Eshhar Z (1993) Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the gamma or zeta subunits of the immunoglobulin and T-cell receptors. Proc Natl Acad Sci 90: 720-724.
4. Garcia-Lora A, Algarra I, Garrido F (2003) MHC class I antigens, immune surveillance, and tumor immune escape. J Cell Physiol 195: 346-355.
5. Ramos CA, Heslop HE, Brenner MK (2016) CAR-T Cell Therapy for Lymphoma. Annu Rev Med 67: 165-183.
6. Kalos M (2011) T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Sci Transl Med 3: 95-73.
7. Porter DL (2011) Chimeric Antigen Receptor Therapy for B-cell Malignancies. J Cancer 2: 331-332.
8. Ding X (2008) Ocular toxicity of fludarabine: a purine analog. Expert Rev Ophthalmol 3: 97-109.

***Corresponding author:** Xiaowei Liu, Center for Infectious Disease and Vaccinology, The Biodesign Institute, Arizona State University, USA, Tel: +4803053662; E-mail: Xiaowei.Liu@asu.edu

Received July 25, 2016; **Accepted** July 27, 2016; **Published** July 29, 2016

Citation: Liu X (2016) Comment on the Current CAR-T Technology. J Immunooncol 2: e101.