Developing strategies to improve efficacy and safety of chimeric antigen receptor cell therapy

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For decades, cancers have been treated with standard treatments, including surgery, radiation, and chemotherapy. However, patients with refractory or recurrent cancers require novel therapeutic modalities. Immunotherapy, an emerging therapeutic option, can harness the components of immune system to fight disease. It represents the future of cancer treatment and its efficacy has been shown even in aggressive types of cancer.

Recent technological advances have made it possible to efficiently transduce transgenes in immune effector cells such as T and NK cells, allowing them to be redirected to target tumor antigens. Genetic engineering of T or NK cells to be armed with chimeric antigen receptors (CARs) have been shown to successfully redirect the specificity of those cells against tumor cells.

Studies on treatment with CAR T or NK cells are growing rapidly. Currently, most clinical success has been achieved using CAR-T cells, especially for hematological malignancies. In 2017, two CD19 CAR T-cell therapies were approved by the FDA, one for the treatments of children with ALL, and the other for adults with advanced lymphoma. However, CAR T-cell therapy has several limitations such as severe cytokine release syndrome, prolonged *in-vivo* persistence, and relapse due to target antigen loss, and the hassle of producing patient-specific products. Therefore, strategies to improve the efficacy and safety of CAR T-cell therapy are required.

Another target antigens have been studied to develop an approach to prevent and treat CD19-loss escapes in ALL. The interleukin-3 receptor α chain (CD123) is one such antigen that is highly expressed on myeloid and B-cell leukemia cells. Thus, CAR therapy targeting CD123 can be a potential alternative approach to treat CD19-loss relapse. In addition, dual CD19 and CD123 targeting CAR-T cell therapy is expected to further enhance the efficacy of CAR-T cell therapy to prevent antigen-loss relapse.

A potential strategy to improve the safety of CAR cell therapy is to use another immune effector cells such as NK cells, other than T cells. NK cells are potential effector cells in cell-based cancer immunotherapy. Human primary NK cells and the NK cell lines have been successfully transduced to express CARs against cancer cells in several pre-clinical trials. NK cells have several advantages as effector cells to carry CARs. First, CAR NK cells might be safer than CAR T cells in clinical use. Second, NK cells can spontaneously kill tumors by recognizing diverse ligands via a variety of activating receptors such as CD16, NKG2D, and NKp30, in addition to killing target cells through a CAR specific mechanism. Third, NK cells have no risk of GVHD, so there is an opportunity to produce “off-the-shelf” products.

This lecture will review the recent effort to develop strategies to improve efficacy and safety of CAR cell therapy.