Novel Targets Brings Possibility for CD19 CAR-T Therapy Relapse After Remission.docx

Bella Smith
Will Complete Remission Possible for CD19 CAR-T Therapy?

As one of the most promising tumor targeted immunotherapy techniques, chimeric antigen receptor T cell (CAR-T) therapy has proved effective in the treatment of a variety of relapsed/refractory (R/R) B-cell malignancies, including but not limited to chronic lymphocytic leukemia (CLL), acute B-cell acute lymphoblastic leukemia (B-ALL), and B-cell lymphoma.

Needless to say, the most successful case of CAR-T is a series of clinical trials targeting CD19 against B cell tumors. CD19 is a cell surface antigen specifically expressed in various differentiation stages of B lymphocytes. The majority of B-lineage malignancies including non-Hodgkin lymphoma cells, chronic lymphocytic leukemia and B-cell acute lymphoblastic leukemia, express CD19. It is therefore considered an ideal target for CAR-T in the treatment of B-cell neoplasms. The results of clinical trials have shown that the cure rate of CD19 CAR-T for acute B-lymphocytic leukemia (B-ALL) has reached 90%.

However, 20% to 30% of patients with leukemia and lymphoma, relieved by treatment with CD19 CAR-T cell therapy, will relapse one year later. The current CAR T therapy is hindered since these cunning tumor cells of up to a third of patients have known to not express targets previously recognized by immunotherapy,
thereby relapsing again, which means that tumor cells escape CAR-T recognition attack by not expressing target/target deletion or target epitope masking.

Fortunately, with the consistent efforts of the researchers, novel possibilities have emerged when the first CAR-T treatment targeting the B-cell activating factor receptor (BAFF-R) on cancer cells successfully eradicated in animal models CD19 treatment-resistant human lymphoma and leukemia cells. Next year, the clinical trial will be launched for patients with relapse after CD19 immunotherapy and is likely to be used as a first-line drug for CAR T-cell therapy.

How does CAR T therapy work? Firstly, T cells are extracted from patients’ blood. Next, immune cells are genetically engineered in the laboratory to identify and invade specific proteins (targets) associated with cancer, for instance, the B cell activating factor receptor BAFF-R. The engineered cells are then reintroduced into the patient's body to start the journey of destroying tumor cells.

On one hand, animal models of human tumors, including Burkitt's lymphoma, Mantel cell and other non-Hodgkin's lymphoma subtypes, and acute lymphoblastic leukemia, treated the BAFF-R CAR T, were observed with significant prolonged
survival and tumor regression after treatment. Particularly, an animal model with human Burkitt lymphoma are cured after a single treatment, with complete tumor regression and 100% long-term survival. On the other hand, animal models with CD19 positive and negative mixed human tumors, are treated with CD19 CAR T cell therapy or BAFF-R CAR T cell therapy, respectively. Results showed that the former one, which is CD19 CAR T cell therapy, has failed, while the other one achieved the eradication of both tumors. It demonstrates that BAFF-R CAR T cells are consistently active against these tumors, while CD19 CAR T cell therapy is greatly reduced in response to recurrent tumors after each case of immunotherapy compared to pre-treatment samples.

At present, CAR-T therapy in the treatment of hematological malignancies has achieved remarkable achievements, but in addition to the treatment of various complications, the recurrence of primary disease is still one of the major obstacles facing the therapy. The clinical efficacy of CD19 CAR-T therapy is expected to be enhanced by screening the ideal target antigen, exploring the best combination of target antigens, optimizing the patient’s own conditions, and exploring the combination of treatment regimens.