Case Study

Identifying specific cytokines that relate to cytokine release syndrome with CAR-T cell therapy

Problem: CAR-T cell therapy can result in severe cytokine release syndrome

Adoptive T-cell therapy is the infusion of T-lymphocytes that can recognize and kill tumor cells in patients. This therapy has become an increasingly popular replacement or combination therapy with standard chemotherapies for the treatment of cancer[1,2].

The most promising form of adoptive T-cell therapy in current use involves the generation of chimeric antigen receptor (CAR)-expressing T-cells (CAR-T). CAR-T therapy involves genetic engineering of T-cells, often derived from the respective patient, in order to produce receptors exposed at the T-cell's surface that can recognize antigens specific to target cancer cells. These receptors are fused to signaling domains that reside within the T-cell that activate its cytotoxic functions. The genetically engineered T-cells are then transplanted back into the patient[3,4]. CAR-T therapy has demonstrated cancer remission rates as high as 80%, which has led to successful FDA approval of CAR-T-based therapy for hematological malignancies[3,4].

While CAR-T therapy has been successful at treating hematological cancers, current treatments still present with multiple safety concerns. One of the most commonly observed adverse effects with patients undergoing treatment is a severe inflammatory response termed cytokine release syndrome (CRS). CRS often presents as fever, tachycardia, and hypotension resulting from excessive cytokines produced by the infused CAR-T cells. In severe cases, patients require mechanical ventilation and high-dose vasoactive medications[5,6]. Therefore, there is recent interest in identifying biomarkers that can predict the safety of CAR-T cell therapeutic regimens[7,8].

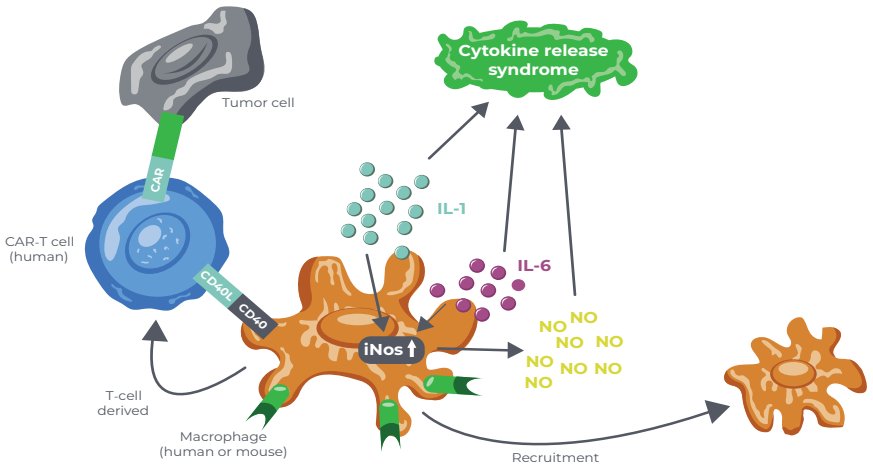

Figure 1. *Graphic relating T-cell therapy to cytokine release syndrome. Adapted from Rooney* et al[9].

Solution: Identify cytokine biomarkers predictive for severe CRS onset

To determine biomarkers for CRS, Teachey *et al.*[10] sought to identify factors that predicted which patients were more likely to develop severe CRS following CAR-T cell therapy. For this, the authors measured the levels of clinical biomarkers, including cytokines in 51 patients, 39 of whom were pediatric, and treated them with an anti-CD19 CAR-T therapy for acute lymphoblastic leukemia. Out of the 51 patients, 94% developed CRS, which was of a moderate to high severity in 28 out of 51 patients.

From this approach, the authors found that levels of 24 cytokines, including a variety of interferons and interleukins, were elevated in the first month following CAR-T cell infusion in patients that later went on to develop severe CRS, but not in other patients.

Using mathematical prediction models, the authors shortlisted three distinct cytokines that were highly predictive for developing CRS in adult patients who received treatment. This approach was even more accurate for predicting CRS onset in pediatric patients who had a different cytokine signature.

To validate the cytokine signatures, the authors conducted a trial on additional pediatric patients and were able to accurately predict which patients would develop severe CRS. Since certain cytokines were more strongly associated with severe CRS, Teachey *et al.* sought to alleviate CRS with an interleukin blockade. This was done by administering interleukin blocking treatment five days after T-cell infusion to 21 of the 28 patients with moderate to severe CRS. This combinatorial approach led to the rapid alleviation of CRS symptoms in 18 patients, including all pediatric patients.

Opportunities for applying the HTG EdgeSeq Immune Response Panel

The study by Teachey *et al.* highlights the need for identifying a diverse set of cytokines for their expression in predicting adverse response to CAR-T therapy. The authors concluded that early-responding cytokines are more predictive of later disease onset.

A stratified approach to researching risk for CRS associated with CAR-T cell therapy requires evaluating the expression profiles of several inflammatory cytokines, often measured over a time course spanning several days. The HTG EdgeSeq Immune Response Panel could be used for such research due to the extensive repertoire of cytokines that can be measured.

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