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Increasing CAR-T Cell Therapy Specificity in Order to Reduce Damage to Normal Cells

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Cancer immunotherapy is an increasingly popular area of research when it comes to cancer treatment. This type of therapy uses the T lymphocyte to engage the immune system in order to fight against cancer. A recent advancement in this treatment is the use of Chimeric Antigen Receptor, or CAR, -T cell therapy which uses synthetically engineered receptors to redirect T-cells to recognize and eliminate cancer cells which express a specific target antigen. This therapy is innovative but does come with certain barriers including potential damage to normal cells and limited effectiveness against solid malignancies. A study from Satoru *et. al* discover that a "double arm" CAR T-cell system improves target-cell specificity, thus reducing damage done to normal cells. This information is key to improving the efficiency of this therapy. Continued research is still needed to further remove the barriers of this treatment.

Key words: CAR-T Cell Therapy, Immunotherapy, Cancer, Immunology

Introduction

Immunotherapy is a growing area of research when it comes to cancer treatment. Immunotherapy focuses on using the T lymphocyte to engage the immune system in order to effectively fight against cancer (Waldman *et. al* 2020). Research on this therapy has been ongoing for the last fifty years and has more recently taken a common place in clinical treatment. There is a new revolutionary type of immunotherapy which is being brought into the spotlight recently which is Chimeric Antigen Receptor, or (CAR), T Cell therapy. This therapy which was approved by the FDA in 2017 uses CARs which are engineered synthetic receptors that are designed to redirect T-cells to recognize and eliminate cells that express a specific target antigen (Sterner *et. al* 2021). These CARs consist of combined parts of the TCR complex and antibodies (Watanabe *et. al* 2018). This is especially useful for those cancers that have become resistant to chemotherapy and radiation or for those that have reached their toxicity ceilings with current treatment (Rogosic *et. al* 2020). This therapy has been revolutionary with great success, but is not without its downfalls. These include limited efficacy against solid tumors, cell-associated toxicities, and for the purpose of this paper, potential damage to normal cells (Sterner *et. al* 2021). More research is actively being done on how to overcome these shortcomings. This research includes a study from Satoru *et. al* which seeks

to improve CAR-T cell therapy specificity which would reduce damage done to normal cells which express the target protein (2020).

Recent Progress

In this study Satoru *et. al* look at ways to increase CAR-T cell therapy specificity in order to expand the target disease which can be treated with this therapy (2020). They first created a specific CAR which was called anti-CD19 mCherry which contained the mCherry fluorescence protein in the cytoplasmic region (Satoru *et. al* 2020). This mCherry fluorescent protein has faster and higher photoactivation as well as better photostability when compared to other proteins (Subach *et. al* 2009). This is likely why this protein was used in this study. This was known as the "effector CAR" which targets a cell-surface protein on tumor cells. They also created anti-CD19 scissors CAR and anti-HER2 scissors CAR which were co-cultured with target cells in order to analyze the target-cell-dependent cleavage of mCherry CAR (Satoru *et. al* 2020). These were the "scissors CARs" which recognize a target protein and induce inactivation of the effector CAR (Satoru *et. al* 2020). This is what is referred to as the "double-arm" CAR-T cell system (Satoru *et. al* 2020). These CARs were then transduced to primary T cells from healthy donors which were then co-cultivated with target cells to measure target-specific cytotoxic activity (Satoru *et. al* 2020). The results of this study showed that this "double arm" CAR-T cell system does improve tumor-cell- specificity which is valuable information when it comes to overcoming the issues with this form of therapy (Satoru *et. al* 2020).

Discussion

Research on CAR-T cell therapy is vital to improving its use in cancer treatment. This study was important for overcoming the barrier of this therapy damaging normal cells by increasing the specificity. This is especially important for solid tumors because of the lack of tumor-specific target antigens (Watanabe *et. al* 2018). For example, CD-19 directed CAR-T cell therapy has become increasingly efficient at treating childhood leukemia and other hematological malignancies, but remains less effective towards solid tumors (Rogosic *et. al* 2020). This is because tumors release an overexpression of tumor-associated antigens which the CAR-T cells recognize. The issue is that these antigens are also expressed in normal amounts in healthy tissue and organs which makes it harder for the CARs to distinguish normal cells from cancer cells (Watanabe *et. al* 2018). This does not mean that all solid tumors cannot be treated with this therapy. For example, some forms of prostate cancer are being treated with CAR-T cells (Yu *et. al* 2019). There are still other shortcomings to be discussed such as the fact that different CAR-T cell products have different rates of toxicity (Messmer *et. al* 2021). These are two areas where further research is needed in order to make this therapy as effective as possible.

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