NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

CAR T Immunotherapy: Engineering the Immune System to Fight Cancer

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Part I – CARs for Cancer

Jesse's cancer was back. He had been diagnosed with B cell acute lymphoblastic leukemia (B-ALL) and had gone through multiple, grueling rounds of chemotherapy. At the time of his initial diagnosis, he was ready for a fight, determined to overcome the illness. His oncologist, Dr. Claire Sanguine, was hopeful for a full recovery after detecting a decrease in the number of cancer cells. Sadly, however, the most recent test indicated the cancer had returned. Now, all Jesse felt was despair. Nevertheless, Dr. Sanguine was still hopeful. She felt that Jesse was a good candidate for a new treatment called CAR T therapy, which had just recently been approved to treat B-ALL.

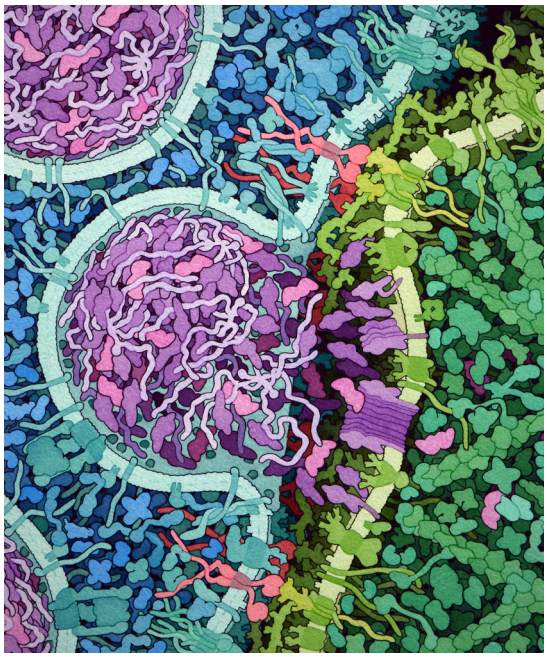

Figure 1. Artistic illustration of an engineered T cell (on left, blue) recognizing and attacking a leukemia cell (on right, green). The CAR molecule (red) binds to CD19 on the leukemia cell. This activates the T cell, which releases perforin (purple), forming pores in the cell surface. Granzymes (magenta) enter through the pore and initiate apoptosis to kill the cancer cell. *Credit:* David S. Goodsell, RCSB PDB, DOI: 10.2210/rcsb_pdb/mom_2017_10, CC BY 4.0.

Questions

1. How is CAR T therapy different from traditional chemotherapy?

2. What does "CAR" stand for? What does the "T" stand for? For Jesse's treatment, where will the "T" come from? Why is the source of the "T" important for organ/tissue rejection?

3. Jesse has a type of cancer called "B cell acute lymphocytic leukemia." What is the normal function of cells that give rise to this cancer?

Part II – A Review of T Cells

Despite his apprehension and low spirits, Jesse showed up to the lab and was hooked up to a machine similar to the one used for his chemotherapy. This time, however, instead of the machine administering drugs to him, the machine removed his blood and seemed to send his blood right back into his body. Dr. Sanguine explained that the machine was removing Jesse's T cells, which would be "reprogrammed" to recognize and destroy his cancer. Jesse wanted to know how T cells worked, and how they would be reprogrammed (i.e., genetically engineered).

Questions

4. Let us review how a normal $CD8^+$ T cell first recognizes an antigen-presenting cell and undergoes T cell activation. Below, draw two cells: a $CD8^+$ T cell on the left and a professional antigen-presenting cell that it recognizes on the right. Include the proteins present on the surface of a normal naïve $CD8^+$ T cell and the proteins on a cell it recognizes. Remember to include important co-stimulatory and signaling molecules involved in activating naïve T cells. Label proteins on the surface of both cells, and include the receptor-associated proteins that become phosphorylated during T cell activation.

5. In your drawing, does the T cell recognize its target cell in an MHC-dependent manner or MHC-independent manner? Explain why.

Part III – Engineering the CAR to Target B-ALL Cells

The CAR that will be expressed on the surface of Jesse's T cells is a genetically engineered protein. It contains various domains of different proteins, with three goals: bind specifically to the intact protein found on the surface of B-ALL cancer cells; insert in the plasma membrane of T cells; and help activate naïve T cells. Let us investigate each of these domains and their role.

Questions

6. B-ALL cancer cells recognized by CAR T therapy are identified by a protein present on the surface of the cancerous B cells. What is this protein? Is this protein present only on cancer cells? What is the normal role of this protein?

7. What is the origin of the extracellular domain of the CAR molecule used to treat B-ALL? Below, draw the complete molecule that is the original source of the extracellular domain of the CAR and label your drawing. Circle the part of the drawing used to build the extracellular portion of the CAR.

8. The CAR molecule contains a transmembrane domain that allows the protein to be inserted into the plasma membrane. The cytoplasmic portion of the CAR molecule contains intracellular domains that can trigger the activation of naïve T cells. What proteins are the origins of these domains? Did you draw the source of these domains in any answers to previous questions?

9. Below, draw two cells: a B-ALL cancer cell on the right and a CAR T cell on the left. Include and label proteins on the surface of the cancer cell that are recognized by the CAR molecule. On the CAR T cell, draw a CAR molecule, label the domains, and indicate the antigen-binding domain of the CAR molecule.

10. When CAR molecules interact with their extracellular target, this leads to a biochemical change to intracellular domains of the CAR protein. What are these domains called? Include the biochemical change in your drawing above.

11. Does the CAR T cell recognize its target cell in an MHC-dependent manner or MHC-independent manner? Is it the same as how a normal T cells recognizes its target cell? Explain.

12. Will the CAR only bind to cancer cells, or will it bind to normal cells as well?

13. How is the gene that encodes for the CAR protein expressed in T cells?

Part IV – Driving the CAR

After a few weeks, Dr. Sanguine informed Jessie that his therapy was ready and it was time to start the treatment. With the support of his family, Jesse had been trying to feel more optimistic. However, Dr. Sanguine could tell he was still very apprehensive so she tried to be positive and encouraging. Wanting to make sure that Jesse knew what to expect with the treatment, she shared that they would be watching him closely for a few weeks, as there could be some significant side effects. Once all of his questions were answered, he was ready for his infusion of CAR T cells.

At first, nothing happened. Around ten days, Jesse began to feel very ill, almost as if he had the flu. He had a high fever, chills, and his blood pressure dropped to dangerously low levels. He feared the cancer was winning but Dr. Sanguine once again assured him that these signs and symptoms resulted from the treatment, not the disease. And his doctor was right; a few weeks later, the fever and chills were gone. So was the cancer.

Questions

14. There are different types of T cells, including $CD4^+$ and $CD8^+$ T cells. What types of T cells are CAR T cells? What will occur when these CAR T cells encounter their target cells?

15. What substances were making Jesse feel ill, causing fever and changes in blood pressure? What is the clinical term for this, mentioned in the articles? Name specific molecules (some of which are mentioned in the articles) and their possible sources.

Part V – The CAR Reaches Its Destination

After lab tests showed undetectable levels of cancer cells, Jesse asked Dr. Sanguine if he might need to return for more treatments. Dr. Sanguine was confident that Jesse's last treatment would continue working for a very long time, possibly his whole life. However, he would have to return to the clinic regularly for immunoglobulin replacement therapy and monitoring for infections he might be more at risk for, post CAR T treatment.

Questions

16. What does Dr. Sanguine mean when she said that Jesse's treatment would likely work for the rest of this life?

17. Thinking about all the cells that are targeted and destroyed by the CAR T cells, what is now the status of Jesse's humoral immune system? Why would he need immunoglobulin replacement therapy? Why would he need to be monitored for infections?

References

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