Neoantigens: The Future of Personalized Cancer Treatment

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Over the last century, there have been numerous advances in oncological research, each one getting us closer and closer to treating one of the most fatal diseases of our generation: cancer. Presently, many treatments may only be effective for a short amount of time and finding long lasting cancer treatments has been a struggle for many patients.[8] Chemotherapy–the use of chemicals to eradicate cancer cells–can be effective yet it kills many healthy cells in the process, leaving patients with painful side effects. Likewise, the most common forms of radiation therapy can also cause damage to healthy tissue, prolonging treatment.[11] Naturally, neither of these two options sound particularly appealing, and while many people do not have the luxury of choice when handed a diagnosis, there are less destructive treatments on the horizon. Immunotherapy, the term for using one's own immune system to fight cancer, is different from other types of treatments as it only attacks tumor cells. Although the immune system's job is to attack foreign cells, tumor cells start out as normal, healthy cells until they proliferate out of control. As such, the immune system does not recognize them as foreign cells. It is for this reason that current immunotherapy treatments are only viable for a short amount of time, with patients having to continually switch treatments to ensure that tumors are not growing. However, recent advancements pertaining to cancer immunology have begun to widen the efficacy and length of treatments.

In recent years, there has been a promising solution to the shortcomings of modern cancer treatment: personalized cancer treatment tailored to the individual. Tailored treatment could provide a solution to some of the issues that come with mainstream cancer therapy. This specificity is achieved by creating fewer side effects and directly targeting only cancer cells.[1] As put by the Journal of Molecular Biomarkers and Diagnosis, "the suitability of this 'one-size-fits-all' approach to cancer therapy is called into question. Precision medicine, the proposed future for the treatment of disease, is based on a tailored approach for selecting therapy at the individual patient level."[2]

The human body possesses a complex immune system with many types of cells. Before speaking on some of the new personalized immunotherapy treatments, a short background discussion about how our immune systems work is needed. There are two main types of white blood cells present in the immune system: T-cells and B-cells. T-cells, which originate in the lymph nodes, recognize foreign intruders and threatening cells within the body and will attack them to reduce harm to the body. B-cells interact with antigens, which are specific foreign molecules that will elicit an immune response. B-cells will recognize certain antigens as foreign and will then produce antibodies (proteins) that will attach to foreign materials and act as a flag down for the immune system to locate and destroy them.[10]

A major characteristic of immune cells is their ability to recognize molecules on the surface of cells, which is the mechanism that personalized immunotherapy treatments take advantage of by using neoantigens. A neoantigen is a new protein that forms on the surface of cancer cells when certain mutations occur in tumor DNA. Neoantigens play an important role in helping the body build an

immune response against cancer cells.[3] Neoantigen-based cancer treatments are revolutionary, as the immune system will be wired to only destroy cells that display neoantigens (cancer cells), and all other cells in the body will be unaffected–a feat that chemotherapy and radiation therapy treatments have not been able to achieve. According to initial studies of neoantigen-based vaccines, scientists have generated a multitude of evidence surrounding "antitumor activity in patients with melanoma", with neoantigens playing a key role in the T-cell immune response against tumor cells.[4] A recent paper published in 2021 completed a study on a group of 729 breast cancer patients, and patients who were reported to have a "high level of neoantigen expression" demonstrated improved survival. Furthermore, neoantigen-based vaccines have been shown to be effective in mouse models for cancers such as skin, colon, and bone cancers.[5] Neoantigens have also been shown to be effective in the clinical realm, as a recent clinical trial completed by the Center for Cancer Research utilized neoantigens in a breast cancer study; in total, they treated six women with metastatic breast cancer using Tumor Infiltrating Lymphocytes (T-Cells that have neoantigens on their surfaces) that were personalized to each patient, and found that "tumors shrank in three of the six women", one of which became completely cancer free after the treatment.[6]

How can medical researchers train an immune system into attacking cancer cells? The first step is to sequence the patient's normal genomic DNA as well as the tumor's DNA. The two sequences are then compared to find mutations within the tumor DNA; these mutations will eventually be the "targets" for the immune system to aid in recognizing cancer cells. In order for a mutation to be an effective target for the creation of neoantigens, the mutation must encode for a protein that is expressed on the surface of the tumor.[9] This protein must also be able to be recognized by the immune system, so an immune response can be generated. Once a mutation that meets these requirements is found, there are a couple of different ways to induce the neoantigen treatment into the patient, including vaccines and T-cell therapy.[7]

In neoantigen based vaccines, the neoantigens identified during mutation analysis are injected into the body and will elicit an immune response from T-cells and B-cells. These immune cells will recognize the neoantigen vaccine as foreign and are programmed to attack any material within the body presenting the specific neoantigen. In the process, they will also attack neoantigen-presenting tumor cells. In T-cell therapy, neoantigens are added to the patient's isolated T-cells in the lab and are grown until the T-cells reach a high enough concentration. T-cells have specific receptors that are programmed to recognize the specific neoantigen sequence that was previously isolated. Once the cells reach this concentration, they will be injected back into the patient and the T-cells will start attacking any foreign materials expressing that specific neoantigen.[7]

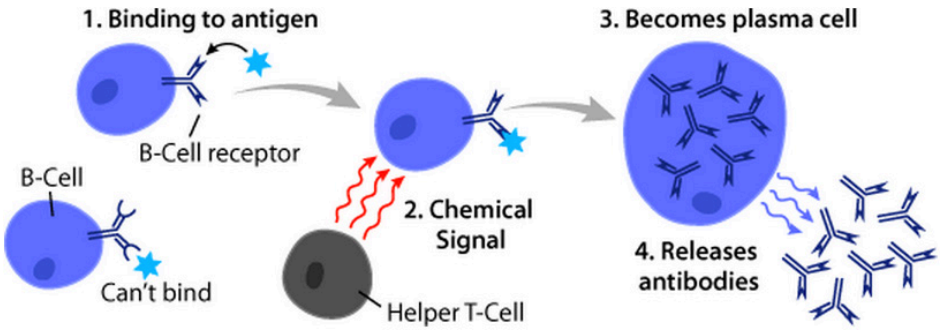

Figure 1: B cells binding to antigens and releasing antibodies.

"A neoantigen is a new protein that forms on the surface of cancer cells when certain mutations occur in tumor DNA."

CONCLUSION

While investigators have made great strides in personalized neoantigen cancer treatments, if widespread use of these treatments is to take place, more research is required on how to produce them on a large scale for many patients. An issue with the current neoantigen treatment research is that it is difficult to find a mutated sequence that can be targeted and expressed as a neoantigen. Because of this, it can take a long time to find a suitable sequence for one patient, and most cancer patients do not have this time to wait.[2] Furthermore, not all patients have tumors that are easily accessible, making it difficult to sequence the tumor DNA, which is essential for neoantigen treatments. Clinical and preclinical trials are currently being completed and are aiming to target these issues. Despite these challenges, the promising research surrounding neoantigens provides a foundation for a new generation of cancer treatments, focused around diminishing harmful side effects and creating more tumor specificity. These treatments will be free of toxic chemicals or harmful radiation, and consequently, cancer patients will eventually have a higher quality of life that is largely pain-free.

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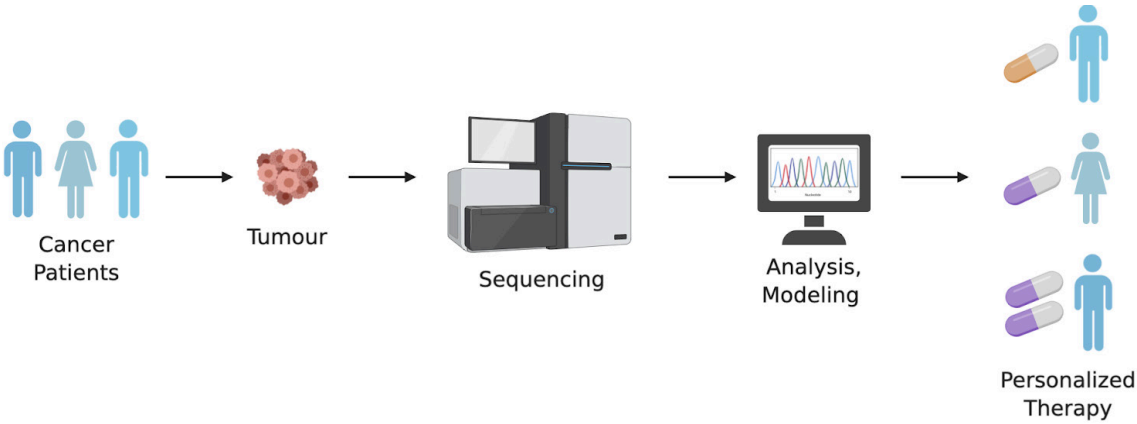

Figure 2: Personalized cancer therapy procedure.

> "T-cells have specific receptors that will be programmed to recognize the specific neoantigen sequence that was previously isolated."

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IMAGE REFERENCES

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