Novel Immunotherapy Adjuvant: Oncolytic Viral Therapy

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Abstract

Through the rise in novel technology in the realm of cancer, science has taken a significant step forward in treatment. Despite such advancements, struggles lie ahead: tumor relapse remains a prevalent issue due to the lack of durable treatments that combat the return of cancer. The following discusses the path of using immunotherapy and oncolytic viral therapy in conjunction to mediate where the other lacks. I propose deriving viruses to target cancer-specific receptors consisting of vaccinated viral antigens to activate an immune response. This approach allows for long-term durability and patient-specific treatment, thus reaching more populations.

Introduction

Dating back to 3000 BC, the history of cancer has been extensive. The first written encounter is in the Edwin Smith Papyrus, where the writer describes an untreatable bulging tumor (Hajdu, 2010). Since then, the human population has struggled to battle this formidable enemy. However, scientists have pieced together a part of the puzzle through many trials and experiments. From current research, the overarching problem, despite the various types of cancer, is the uncontrolled division of the cell. Unregulated multiplication leads to either solid masses, tumors in organ systems, or liquid tumors in the humors.

Fortunately, there has been a drastic improvement in cancer-related technology and treatment. For example, there is a more effective cancer screening system that includes an array of tests. Doctors can either predict or catch cancer in its early stages using physical examination techniques and patient history. Screening techniques include laboratory and genetic tests, which obtain information from the body's interior (Physician Query Data, 2020). After the screening process, multiple treatment options are available, corresponding to the severity and type of cancer. The most popular and effective methods include chemotherapy, surgery, and radiation therapy. Chemotherapy concerns drug use to systematically kill cancer, which differs from other treatments since it is not confined to a local area. Meanwhile, radiation therapy and surgery refer to treatment in a specific area (The American Cancer Society medical and editorial content team, 2019). Surgery targets tumor removal, while radiation therapy utilizes radiation to break DNA, preventing the cancer cells from proliferating and eventually killing the problematic cells. These methods are usually used in conjunction with each other to ensure success for several reasons: enhanced effectiveness through synergy or different levels of effectiveness at specific stages (SEER Training Modules). Moreover, while the aforementioned treatments are popular, drawbacks remain. Drawbacks can include troubling side effects like fatigue, soreness, pain, and increasing risk for other conditions (ASCO, 2021). In addition, it is essential to remember that these forms of treatment, while they can successfully kill cancer, do not provide long-term prevention measures from cancer returning.

Of course, however, there is more to cancer treatment than just these three strategies. Throughout this paper, I will focus on more recent therapies focusing on immunological aspects. Immunotherapy works differently since it utilizes the patient's immune system against the cancer cells. I will also discuss applying oncolytic viral therapy to take advantage of the immune system. This treatment has advantages and disadvantages; however, by the end of this paper, I will discuss ways to mediate its drawbacks and make it more efficient. My result will consist of a

hypothesis based on accumulated evidence from completed clinical trials and an extensive analysis of the application of oncolytic viral therapy.

Immunotherapy

In the last decade, the usage of immunotherapy has become more popular. Still, this practice can be dated to two German scientists, Fehleisen and Busch, with the notice of tumor shrinkage after an erysipelas infection, with the pain perpetrator being *Streptococcus pyogenes* (Dobosz, 2019). Of course, since then, society has dramatically improved this technique with the targeted invention of checkpoint inhibitors and CAR T-cell therapy. However, it is crucial to understand immunotherapy at its foundation. As aforementioned, at its core, immunotherapy either boosts or utilizes a patient's immune system to search for and kill cancer cells. Some sub-treatments under immunotherapy work primarily to slow the proliferation of cancer cells, while others operate under the "search and destroy" mechanism (National Cancer Institute, 2019).

For example, some common sub-treatments are monoclonal antibodies, immune checkpoint inhibitors, and cancer vaccines. Monoclonal antibodies are target-specific antibodies engineered in a lab to mark cancerous cells for the body's immune system to recognize. A prime example is rituximab, which binds to CD20 and marks them for death by the immune system. Another usage of monoclonal antibodies is seen through the blinatumomab binding to CD13, a surface protein on leukemia cells, and CD3, a T-cell surface protein, facilitating T-cells to get closer to and kill the leukemia cells (National Cancer Institute, 2019). On the other hand, checkpoint inhibitors work differently by relieving the "off-switch" on immune inhibitory markers. These markers primarily prevent an overactive immune system by binding to a partner protein and sending an off signal to T-cells. However, immune checkpoint inhibitors can block these markers from sending that off signal in the context of immunotherapy and let the T-cell kill the cancer cell. Some examples of negative regulators include PD-1 and CTLA-4 surface receptors (National Cancer Institute, 2022). While these forms of treatment are more reactive, cancer vaccines offer a preventative solution. For example, vaccines that work to prevent human papillomavirus also protect against HPV-induced cancers like cervical cancer. This same concept applies to Hepatitis B, which leads to a higher risk of liver cancer, but with vaccines that prevent this virus, there is indirect protection against one path to the tumor (Dunn).

All these forms of treatment strive to achieve the common goal of killing cancer and, more importantly, instilling memory in the immune system if the cancer returns. Human cell-mediated immunity creates memory cells when dealing with foreign antigens and invaders. When the virus returns, the body can launch a quicker and more effective attack. This is a prominent selling point for immunotherapy, as it offers long-term protection than other forms of treatment. However, with its advantages, this treatment comes with a significant drawback. It is only effective in a small subset of patients, thus limiting its use broadly. However, I will strive to mitigate this obstacle by taking advantage of oncolytic viral therapy.

Oncolytic Viral Therapy

At its foundation, oncolytic viral therapy uses the modification of viruses to target and bring about an attack on the tumor cells (National Cancer Institute, 2018). Early reports achieved the regression of tumors after the acquisition of viral infections, which led to clinical trials that concerned the infection of humans and observation of whether cancer subsides. A prime example of this dates back to 1904; a 42-year-old woman reported the regression of her

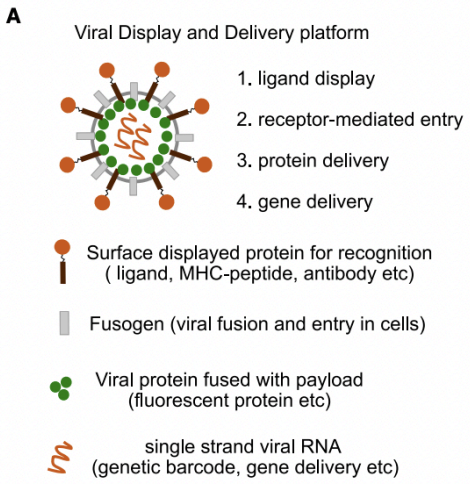
tumor after influenza. Following 1912, the connection between the rabies vaccine and cervical cancer was established. The injection led to the tumor regressing; thus, the concept of using viruses to treat cancer arose (Cao). With little success than with the production of tumor specificity, novel advances in technology have emerged to improve effectiveness.

By using specifically modified viruses made by scientists, oncolytic viruses possess greater precise targeting, long-term durability, and fewer drug-related side effects. Target-specific modified viruses ensure a higher success rate in distinguishing cancerous cells from healthy ones if a cancer-specific marker is available. This leads to less toxicity than traditional therapies like chemotherapy. Moreover, due to the immune system being primed after the viral infection, the adaptive immune system can launch a more effective and quick response if cancer returns, thus providing long-term benefits in maintaining tumor regression (Bell).

However, with such potential advantages come major drawbacks and hurdles to cross; there is a persistent difficulty in finding markers that distinguish healthy and cancerous cells, which is further an obstacle with heterogeneity across and within cancer types. Targeting markers expressed in healthy and cancerous cells is not ideal, as this can result in toxicity. In addition, after the initiation of infection, the immune system may be overactive, leading to dangerously high levels of blood toxicity. I address these drawbacks while capitalizing on the benefits of my hypothesis to use oncolytic viral therapy as an adjuvant to immunotherapy.

Hypothesis

Utilizing elements of oncolytic viral therapy and recent research, I propose taking advantage of viruses and our immune system. To enable this new method, I suggest using technology constructed in the study outlined in the paper "Engineered cell entry links receptor biology with single-cell genomics," which introduces viral technology: "lentiviral-mediated cell entry by engineered receptor-ligand interaction (ENTER)." The paper delves into manipulating ligand-receptor interactions to deliver cargo, including a single-strand viral RNA that can perform protein or gene delivery. ENTER allows for receptor-specificity-based gene delivery (Yu et al., 2022) (Figure A, ref 14). Personalized virus-mediated cancer treatment can come to fruition using the same concepts explored in this study. My hypothesis relies on two core elements: (1) determining the receptor uniquely or highly expressed on cancer cells compared to healthy cells and (2) determining the payload to prime the immune system to kill cancerous cells successfully.



In the paper, the authors discuss targeting B/T-cell antigens; however, by manipulating the receptors based on cancer, cancer treatment can achieve a level of personalization and universality with this method. Take EGFR-positive lung cancer, for example, in which EGFR is seen in a higher quantity indicative of the presence of cancer; the surface displayed proteins can target this (Bethune, 2020, 48-51) (American Lung Association, 2022). This exact mechanism can be replicated with other receptors: HER-2, found in more significant numbers in breast and gastric cancer; mesothelin, which is located in mesothelial cancer cells, one example

being lung adenocarcinoma; or GPR161, which is found to be overexpressed in some breast cancers (Astellas, 2023) (Abramson Cancer Center). Overall, the point is that this component is customizable depending on the patient and the expressed biomarkers.

The payload must be determined after the target receptor has been successfully identified. Deciding what to use determines the efficacy of the entire treatment. Otherwise, the cargo will fail to activate the immune system. In order to ensure a higher chance of success, I propose using strains of previously given vaccines as payload. Using once-exposed strains of viruses that most are vaccinated for allows two things: The immune system is already primed to recognize the “foreign” antigen, and the previously synthesized memory cells are trained to mount a far more effective attack. Determining which strain to use will be different on a patient-to-patient basis. After researching popular vaccines, including tetanus/diphtheria, polio, MMR, hepatitis B, and chicken pox, these will be viable contenders for a patient and allow more patients to be treated. After reviewing the patient’s vaccination records and antibody titers for each virus, the final determination of which strain to use can occur (Centers for Disease Control and Prevention, 2023). Only then the best candidate will be chosen as the cargo. To further ensure an immune response, trials testing the patient’s T-cells against a viral strain in-vitro sample will take place before administering the modified virus in-vivo. Additionally, a simple blood test can track patient progress and success in the treatment by measuring memory T cell expansion in response to viral antigens.

Although the basic concept seems straightforward, complications can arise. A big part of the struggle lies in ensuring that healthy cells that may express the chosen receptor aren’t also targeted. This scenario can simulate an auto-immune response, which endangers the patient’s health. Therefore, the difficulty is introduced when choosing receptors and simultaneously avoiding the death of healthy cells. Fortunately, there is a higher expression of receptors in cancer cells, thus a virus is more likely to infect a cancerous cell, which in turn decreases the risk of healthy tissue dying. Moving forward, clinical trials monitoring how this method fares physically are required to test unforeseen consequences further. If such autoimmune symptoms arise, we can opt for immunosuppressive drugs to quell the immune system, as is done with CAR T cell therapy (Grossberg, 2019).

Conclusion

With the growing prevalence of cancer entwined with the multifaceted challenges, innovative approaches are necessary. Oncolytic viral therapy and immunotherapy provide promising technology that mediates several aspects; however, much is left unexplored. With the application of my proposed hypothesis, treatment can offer more remarkable universality, all while maintaining the benefit of durability. The custom receptor component allows more significant usage among various surface-membrane receptors, while utilization of patient-specific viral antigens ensures a higher success rate. To take this theoretical idea into action, clinical trials, as aforementioned, must follow. The most significant hurdle will be manufacturing the virus to carry one of the specific cargo and primed to the targeted receptor; the modified viral trials will be performed in-vitro against a line of cancer cells according to the chosen receptor and antibody titers, verifying the legitimacy of the hypothesis.

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