**Viruses potential in cancer treatment**

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**Viruses have the potential to lead to an anti-cancer immunity. Through slight genetic modification the viruses may induce immunogenic cell death. The purpose of this study is to determine the ability of three viruses ability to induce immunogenic cell death. These viruses include Semliki Forest virus (SFV), Adenovirus (Ad), and Vaccinia virus (VV). By studying the mechanisms and pathways each of these elicit, we gain more insight for how to design and target tumor cells for better design of viruses for therapy.**

**Introduction**

In the last thirty years the development of recombinant DNA technology has allowed for the identification of essential genes needed in viral replication and the pathogenic mechanisms.3 Numerous viruses are being studied for the potential to be a cancer treatment method. Viruses are capable of selecting, reproducing in, and killing cancer cells. This therapy targets tumor cells and induces an immune response by replication in the cell until it burst, then releasing antigens for the immunogenic cell death.1 This type of treatment is called virotherapy. Oncolytic virotherapy is the use of a virus to therapeutically treat cancer. There are different ways the virus can kill or affect the cell but are all beneficial due to the selectivity. The virus only infects the cancerous cells, while in traditional cancer treatments healthy cells are also killed. Endoplasmic reticulum stress is induced by a viral infection causing the stimulation of type-1 interferons and several other inflammatory cytokines.1 Type-1 interferons are a protein subgroup that regulate the immune system activity. These attract dendric cells to the tumor and stimulate phagocytosis of the cell which equates to priming of anticancer T-cell responses.1 There is an increasing interest in the use of oncolytic viruses. Only one oncolytic virus has been approved by the FDA which is a modified version of the herpes virus to treat melanoma. A recent study by (Jing Ma et al) examined which cell death pathways are activated from infection by three different wild-type viruses which are the natural and non-mutated strains. These include Adenovirus (Ad) serotype-5, Semliki Forest virus (SFV) strain SFV4, and Vaccinia virus (VV) Western Reserve strain. This research tested the capability of each virus to provoke tumor cell lysis and activate an immune response. Adenoviruses are commonly used in clinical research. These viruses are non-enveloped and have a linear double-stranded DNA genome. SFV4 have been engineered to be oncolytic viruses. SFV4 is composed of a single stranded RNA genome and is a neurotropic enveloped virus. This virus has not been evaluated in clinical trials. VV is an enveloped virus and like the (Ad) consists of a double-stranded DNA genome. All of these wild-type viruses stimulate the lysis of tumor cells. This study found that they vary in how each trigger T-cell immune response and dendric cell activation.1 Dendric cells process the antigen matter and express it to T-cells. This study and those like it are crucial to finding better alternatives for cancer treatment. With this information personalized treatments could be formed on an individual basis.

**Recent Progress**

Each of the wild-type viruses were tested against infection of HOS and A549 tumor cells. Wild-type Ad produced no cytotoxic effect when tested in HOS cells, but in A549 cells were killed by the virus on day six after infection. The infection by Ad resulted in a decrease in mitochondrial membrane potential in A549. This suggests that the apoptotic pathways are not activated by Ad. Ad-infection was found to initiate multiple cell death pathways involving activation, autophagy, necreoptosis, and inflammasome.1 SFV4 showed rapid cytotoxic effects in the HOS cells. The susceptibility of A549 was dependent upon the dose and amount of time given between readings. The results from testing SFV4 show rapid induction of cell lysis and also induce apoptosis. VV Western Reserve resulted in quick cell death. Cell lysis by VV induces autophagy and necroptosis in A549. Further studies into the ability of these viruses to stimulate dendric cells to initiate T-cells proved SFV4 to be the most immunogenic. The next most immunogenic was Ad.1 It is known that these three viruses are successful oncolytic agents. This study has taken a deeper look at what makes each virus unique and the contribution it provides to obtain an anti-tumor immune response.

**Discussion**

Ad and VV have been successfully developed as agents to fight cancer in clinical trials and SFV4 preclinically. The contribution and comparison of how these agents cause anti-tumor immune response remains largely unknown. The complexity is a result of virus tropism. The viruses used carried oncolytic virus counterparts that had been genetically modified, which can produce varying infection kinetics. What is known is that each virus facilitated lysis of tumor cells. This leads to phagocytosis and development of dendric cells. The SFV was the only virus to activate important T helper type 1 release, which produced antigen-specific T-cells. The findings in this study are beneficial and provide more insight into better choices for the design of oncolytic viruses centered around immunotherapy. This study concludes that the most beneficial oncolytic viruses are those that do not interfere with immunogenic cell death pathways. This is beneficial because it increases the chance of producing an effective anti-tumor immune response.1 Out of the three viruses studied, the SFV4 was the most appropriate in eliciting an anti-tumor immune response. This study is crucial for understanding what pathway types different viruses affect because that ultimately determines how efficient the virus is at inducing an immune response. Because each cancer case and immune system is different it is hard to see how effective the data truly is. Understanding these viruses more could lead to better selection and genetic modification for an individual’s treatment. The successful clinical trials in immunotherapy have been both miraculous and substandard. While some patients have responded well to various treatments, many more have experienced very little to no clinical response with the same treatment.2 As technology develops, we can gain better insight to how to perfectly modify a virus to an individuals need.

**References**

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