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ORIGINAL ARTICLE

PVSRIPO Effect on Cancer

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Abstract

PVSRIPO, a variant of the poliovirus, is a revolutionary virus that demonstrates key characteristics for oncolytic virotherapy due to its ability to attack glioblastomas. The first criteria that PVSRIPO demonstrates is tumor-targeting tropism. PVSRIPO binds to nectin-like molecule 5 (Necl-5), a poliovirus receptor (PVR), found on different types of cancers such as lung cancer, colorectal cancer, and glioblastomas. This allows the virus to have a high binding affinity to tumor cells. Secondly, after modifying the poliovirus by substituting its internal ribosome entry site (IRES) with the Human Rhinovirus 2's (HRV2) IRES, the poliovirus becomes PVSRIPO, an attenuated version of the virus that will not negatively affect normal cells. Lastly, the most notable effect of PVSRIPO is evoking a host immune response against tumor cells by activating natural killer cells, macrophages and dendritic cells which help the immune system fight tumors.

Introduction

The poliovirus once was considered fatal due to the severe symptoms the virus caused. In many cases it brought about the onset of paralysis, sometimes paralyzing the muscles of the diaphragm which lead to death [1]. The advancement of technology and medicine has brought about a vaccine that has nearly eradicated the virus. In the past, enormous efforts were made to eradicate the virus by creating a vaccine. Now, scientists have repurposed this deadly virus to be a form of cancer therapy.

The conversion of poliovirus from a harmful agent to a therapeutic one is difficult. In general, viruses are hard to manipulate, meaning clinical usage of the poliovirus to treat tumors can be potentially harmful to patients. Complex effects that viruses can incur on the host cell cause complications in treatment. Recent advancements have allowed researchers to genetically modify certain traits of viruses. In relation to the poliovirus, the pathogenicity can now be controlled to some extent [2]. This allows for clinical usage to test the viability of the virus as an agent to treat tumors.

The other potential risks that viruses can incur have not yet been mitigated. For example, there is concern that viruses may cause endogenous gene disruption [3]. For a virus to be considered a viable method for targeting tumors, certain criteria must be met. The virus must not be pathogenic, and its genome must be stable. It must also be capable of targeting tumor cells and creating an immune response specific to those cells. Practical aspects of the virus include stability, production, manufacturing costs, and the overall impact on public health [2]. Researchers must incorporate all of these criteria into a single effective virus. PVSRIPO, a combination of the poliovirus and the human rhinovirus 2 (HRV2), potentially meets these requirements.

PVSRIPO is designed specifically to treat glioblastomas, a common type of brain tumor found in adults. The typical method for treating tumors is using tyrosine kinase inhibitors which cause interference in signaling [4]. Unfortunately, tyrosine kinase inhibitors can cause neurocognitive decline over long durations and have not yet been approved for use on glioblastomas. Many of them have shown no efficacy and have severe side effects [4]. These problems can be solved via PVSRIPO which offers the potential to be more effective at treating glioblastomas as well as provides a lower risk of complications.

The possible benefits PVSRIPO can provide in targeting tumors are unmatched by other methods that are currently being used. The virus can cause tumor cell death as well as adaptive immune responses that specifically target tumors. In addition, PVSRIPO can produce powerful pathogen-associated molecular patterns [2]. These allow for the host's innate immune system to target tumor cells and effectively manage them.

Oncolytic Virus Tumor Targeting

A virus, in general, is only able to attack a host based on the virus's ability to recognize a cellular surface receptor. When recognized, the virus injects its genetic components into the cell, releasing its biological pathogenicity. An oncolytic virus (OV) uses the same mechanism but uses its pathogenicity in a beneficial way. A virus's binding ability to certain cellular surface receptors can be described as tropism. An effective OV should have a natural tumor tropism [2,5]. If it does not, the OV would not bind to cancer cells and will be ineffective or possibly harmful; the OV could attack healthy tissue. OVs have garnered interest because they possess the ability to selectively injected their genetic material into a tumor cell, infecting the cell and possibly leading to cell lysis [6].

PVSRIPO (see below) conforms to the descriptions of an OV due to its tropism for a single cell surface molecule that is highly linked to different types of cancers [7]. The receptor is a cellular adhesion molecule part of the immunoglobulin-like super family called cluster of differentiation 155 (CD155) or nectin-like molecule 5 (Necl-5) [8-10]. More research is needed to completely understand the function of Necl-5, but it is known to contribute to cellular movement and cell to cell adhesion [8]. Discoveries have linked Necl-5 to tumor metastasis [11,12]. Necl-5 stimulates cells to migrate by binding integrins to extracellular matrix proteins which then release migratory signals [11]. Necl-5 has also been shown to reduce both fibronectin adhesion and focal adhesion, leading to an increase in migration [12]. Decreased G0/G1 phase has also been found with the overexpression of Necl-5 which leads to increased cellular proliferation [13], while Necl-5 down-regulation has led to G2/M cell cycle arrest [14]. The overexpression of Necl-5 is found in tumors, but are rarely expressed in normal tissue [14]. Studies have shown Necl-5 has been connected to many different types of cancers including lung cancer [15], colorectal cancer [16], and glioblastomas [17]. The poliovirus due to its natural activity in the central nervous system (CNS) would be most effective attacking neuroectodermal cancers such as glioblastomas [18].

Necl-5, the PV receptor, provides many clinical advantages for PVSRIPO. To ensure the viability of the PVSRIPO, confirming the overexpression of Necl-5 in glioblastomas is paramount. A recently developed assay using antibody CD155 D3G7H provides a reliable method of diagnosing if the level of Necl-5 overexpression warrants the use of the PVSRIPO [19]. 34CD+ hematopoietic stem cells have shown to express Necl-5 and a study has shown PVSRIPO can bind to these stem cells. After infection of the stem cells, PVSRIPO replicates and spreads throughout the body [20].

Experiments using PVSRIPO on glioblastomas have shown positive results. When infecting mice with malignant gliomas, PVSRIPO receded and was eventually eliminated the tumors [7]. Additionally, the genetic composition of the PVSRIPO was unchanged after eliminating the tumor in glioma xenografts [18]. Due to PVSRIPO's effectiveness in mice and xenografts, the OV was introduced into human trials. One study introduced PVSRIPO to ten patients with recurrent glioblastomas. Each patient was given one of five different dosage levels for phase I. Due to extensive symptoms, researchers agreed to place the patients on dose level 2 for much of the trial, leading to promising results [21]. Another trial introduced PVSRIPO to fifteen patients with recurrent glioblastomas. The group given PSRVIPO had a survival rate of 23.3% after twenty-four months, an increased when compared to the 13.7% survival rate of the historical control group [22].

Genetic Recombination of Poliovirus to PVSRIPO

One of the main hurdles in developing effective oncolytic virotherapy is the virus' specificity to cancer and tumor cells. This is due to target cell tropism, the ability of a virus to identify cell features that allow for viral genome entry into an infected host cell (see above) [2,5]. The problem arises when the virus is exposed to normal cells that express receptors for the virus. This leads to normal cells becoming infected with the virus which is not pragmatic for oncolytic virotherapy. For example, the Influenza A virus uses the (HA) protein, a viral hemagglutinin, to recognize sialic acid on glycoproteins and glycolipids of host cells for viral entry. If this virus is used for oncolytic virotherapy, then normal epithelial cells of the upper respiratory tract of human patients, which also contain sialic acid on glycoproteins and glycolipids, will be simultaneously infected with influenza A [23].

Despite this hurdle in oncolytic virotherapy development, recent molecular virology progress has shown that attenuated or weakened herpes simplex virus 1 and attenuated neuropathogenic poliovirus, *in vitro*, both display a paucity of negative neuropathogenicity in animal models of nonhuman primates and mice [24,25]. PVSRIPO or the oncolytic recombinant poliovirus/rhinovirus is synthesized by replacing its Internal Ribosomal Entry Site (IRES) [26] with an analogous IRES from HRV2 [27]. This causes poliovirus to be a strong candidate for attenuation, meaning the oncolytic recombinant poliovirus/rhinovirus or PVSRIPO can be weakened to the point where it will not detrimentally affect normal cells. PVSRIPO also has a higher neuronal incompetence than its' predecessors, which means that despite being able to enter normal host cells, it will not irreversibly affect the CNS cells of the host [27]. Indicating that the conditions limiting PVSRIPO proliferation in the normal CNS are not present in gliomas and tumors [28].

PVSRIPO is more stable and has better diminution that its' precursors in oncolytic virotherapy due to the substitution of the poliovirus' original IRES for the HRV2 IRES. This halts the poliovirus' intrinsic ability to recruit a specific helicase complex, (eIF4G:4A:4B), whose function is to unwind the viral untranslated regions to be translated in normal cells [28,29]. This method of functional integration of heterologous HRV2 IRES in PVSRIPO is considered more stable, and therefore more effective than its poliovirus point mutation precursors because it is a naturally occurring method denying helicase complex (eIF4G:4A:4B) recruitment. An unnatural mutation can lead to degeneration back to the wild-type poliovirus, which infects normal host cells in the patient [18]. Results further illustrate the substitution of the Poliovirus IRES for the HRV2 IRES in PVSRIPO results in successful attenuation of the virus in primates [11]. The diminution of the Poliovirus in PVSRIPO allows for viral growth in glioma cells, supporting the eradication of tumor cells and halt of tumor growth while demonstrating poor proliferation in normal neuronal cells in animal models [7,25].

Host Immune System Response in the Presence of Cancer

While safety and attenuation of the virus is a major criterion for use in clinical oncolytic virotherapy, another focus of oncolytic virotherapy is the ability of the virus to elicit a host immune response to the tumor cells, known as immunogenicity. The immune system response to cancer is one of the integral components of cancer development. The two types of immunity, innate and adaptive both have methods of handling cancer. Innate immune cells, such as phagocytic leukocytes, dendritic cells, and circulating plasma proteins can contribute to cancer development [30]. For example, innate immune cells can cause the induction of DNA damage by the production of radical oxygen species, while a profusion of infiltrating macrophages and neutrophils can cause an increase in angiogenesis, leading to tumor growth [30]. Adaptive immune cells like B and T lymphocytes arrest cancer growth by either inhibiting tumor growth through cytokine-mediated lysis of tumor cells or antitumor cytotoxic-T cell activity. Conversely, adaptive immune cells can also promote tumor growth by suppressing the antitumor cytotoxic-T cells and increasing inflammation in the tumor, in turn increasing tumor angiogenesis [30].

Recent empirical developments distinctly elucidate that tumors which develop in the host are not deficient in immune cells, but on the contrary, characterized by an extensive influx of innate immune cells, such as macrophages, mast cells, and plasma proteins. A consequence of this extensive influx of innate immune cells is further promotion of tumor growth. These developing tumors ultimately grow because of their ability to halt and avert some adaptive immune responses like antitumor cytotoxic-T cells while simultaneously promoting other adaptive immune responses like tumor angiogenesis [31].

Host Immune Response in the Presence of Cancer Infected with PVSRIPO

The first step in initiating host immune response is the ability for PVSRIPO to target the lone PVR, Necl-5. While Necl-5 is a cellular adhesion molecule expressed during embryonic development in normal cells, the substitution of the HRV2 IRES in the poliovirus allows the PVSRIPO to deny recruitment of the helicase complex (eIF4G:4A:4B) in normal cells. There are also PVR found on mononuclear cells making them highly prone to poliovirus infection which can then differentiate, producing macrophages and dendritic cells with powerful innate and adaptive immune responses to tumors [32]. Attenuation of the poliovirus by denying recruitment of the helicase complex (eIF4G:4A:4B) prevents the expression and propagation of the virus in normal host cells while allowing rapid viral expressions in tumor cells, such as glioma cells [28,29].

Once infected with the virus, the tumor attempts to generate antiviral measures by producing signals for proinflammatory stimulation (PAMP), but most viral infections have evolved a way to divert or halt the PAMP. This effectively counteracts the antiviral response by the tumor cells [33]. The tumor can also produce antiviral cytokines and interferons in response to a viral infection. This response would drastically reduce the viral population, eliminating the PVSRIPO and hindering oncolytic virotherapy [34]. The most exciting prospect of oncolytic virotherapy, namely PVSRIPO, is its ability to induce an immune response from the tumor. When infected with PVSRIPO, the tumor would release antiviral cytokines and interferons to destroy the virus, but also inadvertently destroy itself and recruit additional antitumor effectors to destroy the remaining tumor cells [34]. This illustrates the importance of the virus' tumor tropism, and the tumors ability to build antiviral responses. By developing a way for the virus bypass the tumors' innate defenses, the virus can effectively shut down the tumor cells, while concurrently evoking a host immune response.

PVSRIPO is a novel virus being tested in oncolytic virotherapy because it recruits the host's immune system into action to reduce tumor expression and expansion. For example, CD226 is a poliovirus-like receptor that interacts with Necl-5 and stimulates a T cell response which promotes an anti-tumor response [35,36]. Conversely, CD96 is another poliovirus-like receptor that negatively regulates natural killer cells, thus performing an antibody blockage of CD96 and promoting anti-tumor response [35]. Cyclophosphamide (CPA) is an alkylating agent used in cancer treatment and an immunosuppressive agent utilized in autoimmune disorders. CPA inhibits viral neutralizing antibody formation, allowing for easier delivery of PVSRIPO to the tumor microenvironment [34]. In addition, CPA also can be used as an immunosuppressant, allowing PVSRIPO to replicate at a faster rate in infected tumor cells [34]. The reason PVSRIPO is a promising candidate for clinical oncolytic viral therapy is its lack of ability to defend against a host immune response, while still effectively infecting tumor cells and having a potent immunogenic response.

Conclusion

PVSRIPO has shown promise in becoming an oncolytic virus used in a clinical setting. It matches many of the necessities needed to be an effective oncolytic virus such as a tumor tropism, safety and specificity in genetic recombination, and the

ability to induce a host immune response to fight tumors. The clinical use of PVSRIPO in human trials has exciting results. Patients introduced to PVSRIPO have shown greater survival rates compared to the historical control group. Many adjustments need to be made for this oncolytic virus to become a commonly used treatment for glioblastomas. Determining the correct dosage on a case-by-case basis being the chief problem for the use of PVSRIPO. Despite the potential drawbacks, the possible effectiveness of PVSRIPO as an oncolytic virus makes it difficult not to continue pursuing additional clinical research.

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