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Poliovirus Attenuated Strains as a Possible Candidate for Cancer Therapy

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Abstract

The understanding of cancer continues to expand and with the growing urgency to find effective treatments, the discovery of medications that can disrupt the disease's aggressiveness holds immense importance. Live attenuated viral vaccines and oncolytic virotherapy offer promising avenues in cancer treatment. These vaccines and therapies work in various ways, including serving as vehicles to deliver inflammatory and immune-modulatory cytokines, presenting tumor-associated antigens, triggering "danger signals" to alter the tumor microenvironment, and selectively infecting cancer cells while sparing healthy ones. Clinical trials have explored the potential of several viruses for cancer treatment, with the genetically modified herpes virus, *Talimogene laherparepvec*, showing promise in melanoma treatment. The attenuated strain of Poliovirus, such as type 1 (Sabin), is known for its success in poliomyelitis vaccination and is now emerging as a novel option for cancer treatment. It employs multiple mechanisms to combat cancer, such as inducing tumor cell lysis through viral replication or the production of lethal viral proteins. Poliovirus is a prototype of the Entero-virus genus in the *Picornaviridae* family and is notorious for causing poliomyelitis in children due to its affinity for spinal cord motor neurons. Globally, live-attenuated (Sabin) and killed (Salk) vaccines are utilized to control Poliovirus. **In conclusion,** this study showed the potential of the polio vaccine as a viable option for cancer treatment, emphasizing its origin, potency against cancer, and its interaction with the immune system.

Keywords: Cancer therapy, immunity, Poliovirus, vaccine.

Introduction

In 1988, the World Health Organization (WHO) decided to eradicate poliomyelitis by the year 2000, and since then, there has been a significant decrease in the incidence of the disease. According to (1, 2), the Poliovirus is a small, single-stranded RNA virus with an icosahedral protein coat infecting humans and animals. It typically enters the body through the nose and pharynx, where it rapidly multiplies in the epithelial cells of the pharynx and gastrointestinal tract; it belongs to the *Picornaviridae* family and falls under the genus *Enterovirus*, which includes the common *picornavirus* (*PV*). The virus primarily spreads through respiratory and fecal-oral routes. The majority of infected individuals experience minimal or no symptoms, while approximately 0.1–1% develop paralytic poliomyelitis, commonly known as Polio (3). There are three wild *PV* serotypes: WPV1, WPV2, and WPV3, with only one serotype

immune to heterologous serotypes. While apes and old-world monkeys can be experimentally infected, humans are the only known natural hosts for Poliovirus (4).This review study intends to focus on various aspects of the Poliovirus genetic structure and the possibility of using it as cancer therapy.

The Poliovirus's genetic structure

The poliovirus structure comprises a positive-sense, single-stranded (SS) RNA virus measuring approximately 30 nm in diameter. Its virion consists of a non-enveloped icosahedral capsid containing sixty copies of four capsid proteins: VP1, VP2, VP3, and VP4. These proteins encapsulate a single strand of messenger-sense RNA (5). The RNA genome of the Poliovirus is approximately 7.4 kilobases (kb) in length on average. The variability in genome length arises from the heterogeneity of the 3'-terminal poly (A) tail (4). Figure. 1 delineates the crucial domains of the poliovirus genome. These include the 5'-terminal covalently linked protein VPg (3B in the polyprotein), the extended 5'-terminal non-translated region (5'NTR) housing the cloverleaf structure (vital for genome synthesis), and the internal ribosomal entry site (IRES) responsible for initiating the polyprotein (indicated by the open box) at nucleotide position 743 (6, 7). The polyprotein is divided into three domains (P1, P2, P3), with P1 serving as the precursor to the four capsid proteins VP1–4, while P2 and P3 specify replication proteins. The essential cis-acting (RNA) replication element is mapped to the coding region of P2. The 3' non-translated region (3'NTR) comprises two stem loops and the 3'-terminal poly (A) tail, which varies in length (6).

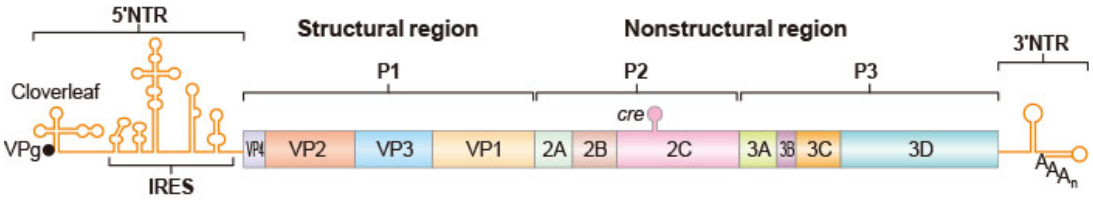

Figure 1: The essential domains of the genome of Poliovirus (7).

Infection, Entry, Replication, Assembly and Immune Avoidance of Poliovirus

In humans, poliovirus infection typically begins with the oral ingestion of the virus. After entering the body, the virus travels to the intestine, where it locates a cell with the appropriate receptor, thus initiating infection. Subsequently, the Poliovirus undergoes replication within the alimentary tract (8).The Poliovirus enters the host cell via receptor-mediated endocytosis, where it binds to the poliovirus receptor (PVR)/CD155 on the host cell's surface. This interaction triggers a rearrangement of capsid proteins (6, 9). The VP1 capsid protein becomes integrated into the plasma membrane, forming a protein channel through which the RNA genome is released into the cellular cytoplasm. Once inside the cytoplasm, the viral RNA acts as messenger RNA (mRNA) and undergoes translation utilizing the host cell's machinery. This process leads to the synthesis of a single polyprotein, which is co-translationally processed into four capsid proteins and seven

nonstructural proteins, namely 2A, 2B, 2C, 3A, 3B, 3C, and 3D (10). These proteins play vital roles in viral replication. The initiation of virus-specific translation begins when ribosomes enter the internal ribosome entry site (IRES) within the 5′ noncoding sequence of the RNA (6). After translation, the viral genome undergoes replication, producing positive-sense copies of the original genome. This replication process involves generating multiple negative-sense copies, which serve as templates for synthesizing positive-sense strands. The protein VPg acts as a primer for both positive and negative sense strands. As replication progresses, viral proteins assemble into a pentameric intermediate, which later transforms into an empty capsid containing 60 copies of VP0, VP3, and VP1. During this assembly process, five copies of VP1, VP3, VP2, and VP4 form the interior surface of the viral capsid. Each capsid encapsulates a copy of the genomic RNA, forming the virus particle (10, 11).Subsequently, the newly synthesized poliovirus virions are released from the host cell through cell lysis into the bloodstream. The virus spreads from the initial replication sites to nearby lymph nodes (cervical and mesenteric) and the bloodstream, potentially infecting extra-neural tissues and amplifying viremia. Polioviruses can breach the intestinal epithelium barrier and traverse the blood-brain barrier to access the central nervous system (CNS), particularly the spinal cord, causing motor neuron destruction and triggering acute paralytic poliomyelitis (12). Poliovirus employs two primary strategies to evade the immune system:

Firstly, it can survive the harsh acidic conditions of the stomach, allowing it to infect the host and spread throughout the body via the lymphatic system; secondly, its rapid replication rate outpaces the immune response, overwhelming host organs before an effective defense can be mounted; and thirdly: by altering its surface proteins, particularly the capsid proteins, through antigenic variation, the virus avoids detection by the immune system.

It also suppresses the interferon response, which is vital for antiviral defense, and tends to replicate in immune-privileged sites like the gastrointestinal tract and lymphoid tissues. Through invasion of nerve cells and manipulation of host cell defense mechanisms, Poliovirus can establish persistent infections, contributing to its capacity to induce paralytic disease (7, 12).

Historical Overview of Poliovirus Vaccines

Polio vaccines are essential for preventing poliomyelitis (polio). There are two main types: the inactivated poliovirus vaccine (IPV), administered via injection, and the attenuated (weakened) poliovirus vaccine (OPV), administered orally. The World Health Organization (WHO) advocates for complete vaccination of all children against polio. These vaccines have played a crucial role in eradicating polio from much of the world, significantly reducing reported cases from approximately 350,000 in 1988 to just 33 in 2018 (13).

Research into the attenuated live poliovirus vaccine began in the early 1950s, following trials led by Dr. Hilary Koprowski, which demonstrated successful immunization of volunteers. Subsequent investigations by Koprowski, Cox, and Sabin explored various attenuated strains as potential vaccine candidates. It was established that the immunogenicity of the live attenuated oral poliovirus vaccine (OPV) was not contingent on its neurotropic capacity (14). In 1957, the World Health Organization (WHO) established the Expert Committee on Poliomyelitis to delineate scientific and ethical protocols for conducting clinical trials. It includes defining the criteria for selecting strains and outlining the requirements for attenuation in developing poliovirus vaccines (15). Between 1957 and 1959, the efficacy and

safety of live oral poliovirus vaccine (OPV) were evaluated in increasingly larger populations, with the number of participants reaching the millions by the spring of 1959. In 1959, the top candidate strains, developed by Cox and Sabin, underwent independent evaluation by Dr. Joe Melnick, a renowned virologist. His assessment conclusively demonstrated the superior safety of the Sabin strains, prompting the United States Surgeon General to endorse their use (16) officially. Between 1957 and 1959, the efficacy and safety of live oral poliovirus vaccine (OPV) were evaluated in increasingly larger populations, with the number of participants reaching the millions by the spring of 1959. In 1959, the top candidate strains, developed by Cox and Sabin, underwent independent evaluation by Dr. Joe Melnick; his assessment conclusively demonstrated the superior safety of the Sabin strains, prompting the United States Surgeon General to endorse their use (17) officially.

When Sabin OPV type 3 was first licensed in the United States in 1961, approximately 150 million individuals worldwide had already received Sabin vaccine strains. However, no traditional efficacy studies were conducted for Sabin OPV strains for various reasons. One significant challenge was the ethical constraint against withholding the inactivated polio vaccine (IPV), which was licensed in the United States in 1955 and provided protection against the Poliovirus. In the absence of randomized trials, evaluations were based on comparisons between vaccinated and unvaccinated groups or geographical areas after the introduction of OPV (18). Identifying suitable comparison groups, particularly those without pre-existing immunity, posed a challenge, especially in tropical regions where polioviruses were prevalent in infancy. In such areas, it was practically unfeasible to identify a nonimmune group of sufficient size and age representation through serological testing. Additionally, in some temperate countries where early poliovirus infection was less common, there was the complicating factor of previous immunization with inactivated polio vaccine (IPV) (19). However, Other factors that needed consideration included:

1. The natural fluctuation of poliovirus transmission from one season to another and from year to year.
2. The prevalence of other enteroviruses that could interfere with the vaccine's effectiveness.
3. The person-to-person transmission of vaccine strains could affect the observed protection of Sabin strains in comparisons between vaccinated and unvaccinated individuals.

Due to the challenges in designing efficacy studies, the most reliable data on the effectiveness of the Monovalent Oral Poliovirus Vaccine (MOPV) came from seroconversion studies, which assessed the immune response elicited by the vaccine. Protection was typically defined as the presence of detectable antibodies in individuals who previously tested negative for them. The ideal participants for vaccine studies were those "triple negative," meaning they were susceptible to all poliovirus types without any confounding cross-protection induced by a single type. However, since individuals meeting these criteria were relatively rare, seroconversion studies mainly involved individuals susceptible to the administered vaccine types but not necessarily to other types (20).

Mechanism of Poliovirus vaccines against Tumour Cells (2Apro)

The oncolytic Poliovirus possesses a unique capability: replicate within tumours while highly targeting specific tissues. This property is particularly advantageous for oncolytic tumourtherapy. The outlined strategy aims to capitalize on this feature to achieve two main goals: directly destroying tumour cells and triggering the host immune system. Poliovirus

infection induces rapid cell death and lysis in susceptible transformed cells. Although several early events in the viral life cycle may contribute, the production of the viral 2A protease (2Apro) plays a critical role in causing host cell death. 2Apro facilitates the suppression of gene expression mechanisms in host cells and promotes the translation of viral components by rapidly cleaving essential elements involved in mRNA export and translation processes (21). 2Apro exhibits potent cytolytic capabilities, as it alone is sufficient to induce cell death. The Poliovirus has a straightforward life cycle due to its RNA-based structure. Instead of establishing intricate parasitic relationships with host cells, the Poliovirus rapidly commandeers and destroys them to enhance its spread. Translation of viral proteins can commence immediately upon exposure of the viral RNA, making this step crucial as it allows the virus to anticipate and counteract host cell defences. This step can be considered the rate-limiting step in the virus's life cycle. The viral 2Apro is the first non-structural polypeptide generated by the Poliovirus. Its proteolytic effects shut down host cell gene expression, curtailing antiviral responses relying on protein synthesis. The brief yet impactful interactions of the virus with host cells prompt robust host defences against infected or lysed tumours. Extensive research has been dedicated to elucidating the molecular mechanisms behind selective tumour cytotoxicity, defining tumour cell targeting mechanisms at the molecular level, and developing non-pathogenic poliovirus recombinants (22).Intra-tumoral viral injection, which induces tumour-selective cytotoxicity, can lead to cancer cell death and potentially reduce neoplastic lesions. The presence of localized virus-induced inflammation may trigger immune responses, including infiltration by neutrophils and other immune cell populations. This process could be crucial for boosting anti-tumour immunity and effectively slowing the spread of cancer cells (23). The dual role of tumour-associated neutrophils, which can both promote and restrict tumour development, resembles the behaviour of macrophages. However, upon encountering a pathogen, neutrophils are believed to initiate inflammatory and cytotoxic activities that are harmful to tumour growth. Figure 2 provides an overview of the mechanism of action of oncolytic Poliovirus (24).

How Does Polio Target Cancer?

The anti-neoplastic potential of oncolytic Poliovirus (PV) immunotherapy hinges on two fundamental aspects: receptor binding and translation of the viral genome. However, a significant challenge for oncolytic viruses (OVs) is their need for specific tropism to effectively deliver the immune-activating and lytic viral payload to the intended tumor target (25). This process ensures the release of tumor-specific antigens, coupled with the adjuvant effect of viral pathogen- and host cell danger-associated patterns (P/DAMPs), along with the activation of co-stimulatory antigen-presenting cells (APCs), following innate antiviral activation in situ. Prior to these events, which facilitate the inflammatory killing of cancer cells by PVSRIPO, the virus must initially bind to its receptor, CD155, also referred to as the PV receptor (PVR) and Nectin-like molecule 5 (Necl-5) (26). CD155 is a transmembrane protein belonging to the immunoglobulin superfamily. Besides its role as a receptor for Poliovirus (PV), CD155 also acts as a ligand for the DNAM-1 (CD226) activating receptor found on natural killer (NK) cells and a subset of T cells. The interaction between CD155 and DNAM-1 has been implicated in the destruction of tumor cells by NK cells. Tumors may exploit it to evade NK and T cell-mediated anti-cancer immunity. CD155 is commonly overexpressed in solid tumors such as GBM (glioblastoma multiforme), where it may contribute to tumor invasiveness and spread (27).

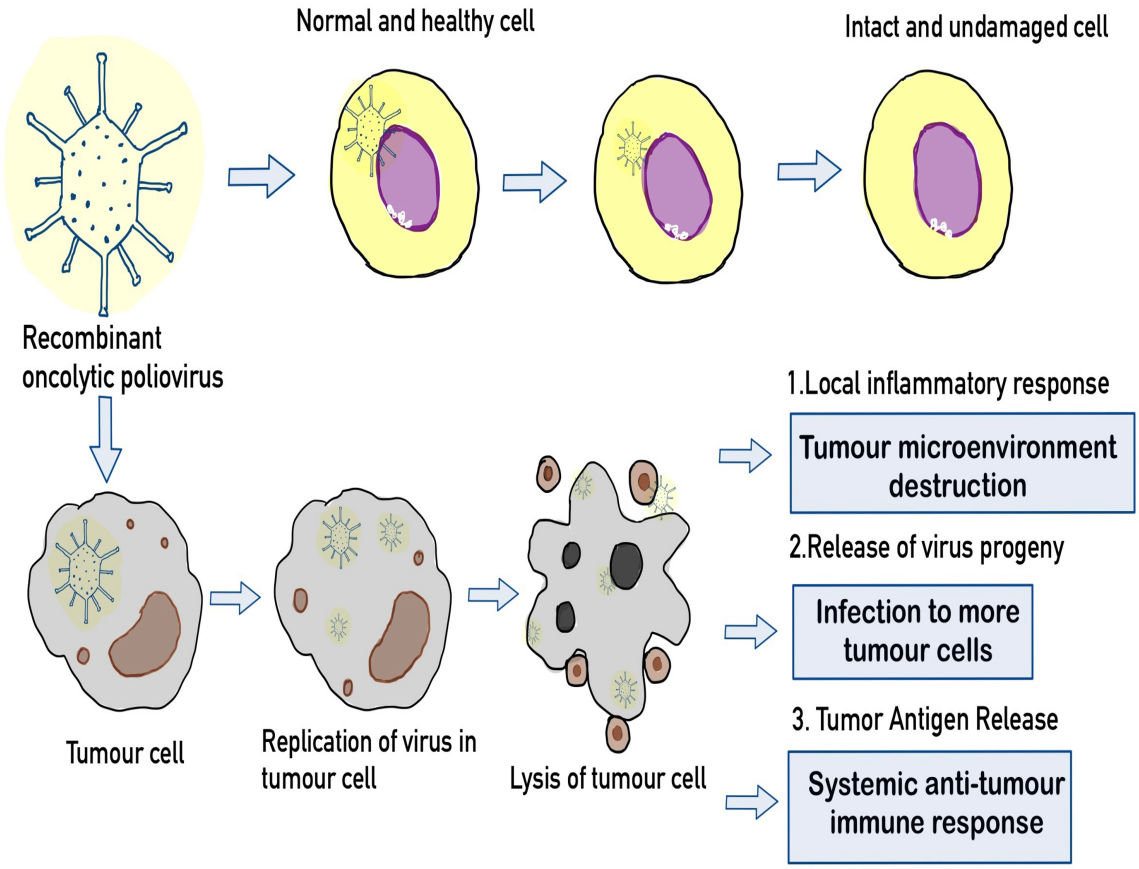

Figure 2: Mechanism of recombinant oncolytic Poliovirus against GBM tumor cells (24).

The upregulation of CD155 has been associated with tissue injury/repair processes and the DNA damage response. CD155 is also expressed in antigen-presenting cells (APCs), making them vulnerable to Poliovirus (PV) infection. Interestingly, this infection is limited in its effects, non-lethal to the APCs, does not impair their functions, and results in the release of pro-inflammatory cytokines. When PVSRIPO targets tumor-associated APCs, it may induce pro-inflammatory effects in the tumor stroma, such as the M1 polarization of tumor-associated macrophages. Considering the significant heterogeneity observed in solid tumours, it is improbable that every cancer cell within a tumor expresses CD155. Therefore, since PVSRIPO primarily drives tumor regression by stimulating an anti-neoplastic immune response rather than through the direct lysis of bulk tumor cells, limited cytolysis of some tumor cells may still be sufficient for effective therapy (28).

Conclusion

The current study showed that physicians' and patients' acceptance of a novel clinical treatment, along with considerations of treatment efficacy and safety, represent significant challenges in implementing new treatment strategies. It also showed that vaccines approved by the World Health Organization (WHO) play a crucial role in bridging the gap between these strategies and their potential application. Attenuated poliovirus vaccines, which can target human cells, offer significant advantages over other therapies that may have severe side effects on non-cancerous tissues.

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Competing interests statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties. No writing assistance was utilized in the production of this manuscript.

Ethics statement

All experimental data were collected in accordance with approved guidelines.

Author contributions

Conceptualization, software, methodology, formal analysis, validation., investigation, resources, data curation, writing—original draft preparation, writing—review & editing ; Qasim A.J. visualization, supervision, project administration, funding acquisition ; Zeadan; A. M. Both authors have read and agreed to the published version of the manuscript.

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