Editorial

Recombinant poliovirus for cancer immunotherapy

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Introduction

For decades, the treatment of cancer, considering origin and staging, has been based on the tripod: surgery, chemotherapy, and radiotherapy. In recent years, target therapy, hormone therapy and immunotherapy have gained prominence. In breast cancer, for example, treatment progression has moved from Urban's surgery to conservative treatments, with the introduction of target therapy and hormone therapy, associated with radio-chemotherapy. Another point is the actual change in breast cancer staging this year, since a historical factor in staging—the larger the tumor size, the higher the staging and the worse the prognosis—is no longer an oncology paradigm.

The immunology of cancer has shown interesting results. After the 1990s, boosted by technical developments, the immunological knowledge had a consistent evolution. To cite some point, the systemic immune status or lymphocytic infiltrate in the tumor stroma may influence the prognosis. Cancer immunotherapy is a new frontier of knowledge and may lead in the future as the fourth therapeutic weapon with the effectiveness of the current therapeutic tripod.

Studies indicate that pathological mechanisms that allow the tumor escape from the immune system recognition can be reversed. Immunotherapies against cancer may offer specific treatment for tumors and reverse tumor immunosuppression through novel cytotoxic and antitumor immune responses (1).

Ways to reverse the tumor immunosuppressive environment are needed, as this favors the tumor escape mechanism, compromising the antigen presentation, production and effective antitumor response of T cells (2).

Immunotherapy with virus is believed to involve the stimulation of an innate immune response capable of leading to an adaptive immune response with its specialized and specific cells. Likewise, it occurs in the anti-viral and antitumor responses, where mainly CD8 T cells act more directly in the target cell through the secretion of enzymes that induce cell death, interrupting viral dissemination (2). Thus, the activation of the intracellular pathways of innate immune signaling within a tumor would increase the presentation of antigens. The expression of co-stimulatory molecules would lead to a Th1 response and to the activation of cytotoxic T cells capable of targeting and killing cancer cells (3).

In a clinical perspective, viruses are extremely complex biological agents that carry a number of different activities in their target tissues. The ability of many viruses to enter, bind, replicate, and kill cancer cell lines *in vitro* has termed them as "oncolytics" (4). The idea seems modern and promising, but in reality, it has nothing new. The use of virus immunotherapy to treat people with cancer was first suggested many years ago. In 1949, 22 patients with Hodgkin's disease received immunotherapy with hepatitis virus (5). From this date until the 1980s, several immunotherapeutic trials with attenuated or wild-type viruses were performed in attempts to treat cancer (6).

However, these viruses were not found to be useful as therapeutic agents because, at that time, no method was known for controlling virulence and still retaining viral replication in cancer cells (7).

Genetic engineering with its modern techniques has increased knowledge about the structure and functionality of viral genes. The method of development of oncolytic viruses, usually DNA viruses, requires manipulation of the viral genome with the generation of a non-pathogenic virus (7). Experiments carried out in both mice and humans suggest that immunotherapy with oncolytic viruses may increase the immune response against tumor cells, as well as stimulate their immunogenic death (8). These stimuli generate innate antiviral responses (type I interferons—IFNα, β) within the tumor and present powerful pathogen-associated molecular patterns (PAMPs). In addition, generation of pro-inflammatory patterns in the tumor stroma and enlistment of adaptive immune responses directed against the virus-infected tumor may occur. To generate an efficient response, such viruses must be capable of reversing the immunosuppressive tumor microenvironment, having genetic stability after replication within that tumor environment, being non-pathogenic, and causing the death of tumor cells by the virus infected even in the presence of activation of an innate immune response (9). An example of an oncolytic virus is poliovirus, an agent that causes polio in humans and has shown promise in tumor therapy. It belongs to the genus Enterovirus, a genus in the family Picornaviridae, composed of serotypes I, II and III (8).

The recombinant oncolytic poliovirus PVSRIPO

PVSRIPO is the name of the live attenuated poliovirus type 1 (Sabin) vaccine that carries a local heterologous internal ribosome entry site (IRES) of the human rhinovirus type 2 (HRV2), i.e., the IRES in poliovirus was replaced by human rhinovirus type 2 IRES (HRV2). This replacement of IRES in PVSRIPO is associated with profound neuroattenuation, in particular the inability of PVSRIPO to cause polio or meningoencephalomyelitis after intracerebral inoculation, and to avoid neurovirulence. This neuroattenuation constitutes the basis for the biosafety of PVSRIPO, making it non-pathogenic (4,10,11).

The main reason for the research of clinical applications of PVSRIPO is the tropism for CD155, a poliovirus receptor also known as Nectin-like molecule 5 (Necl5). This is an onco-fetal cell adhesion molecule belonging to immunoglobilun-like superfamily (12), almost universally expressed in malignant cells of solid neoplasia (11,13), as well as in myeloid and endothelial cells (12). Expression of CD155 in solid tumors means that neoplastic cells in such lesions are susceptible to PVSRIPO infection (14).

The poliovirus is related to the innate system of response to the host antiviral interferon, being the main member of the enteroviruses. This is a decisive factor in the immunogenic mechanism of PVSRIPO (3). In addition, tumoral infection with PVRSRIPO triggers a series of acute inflammatory events that lead to an abundant immune cell invasion, resulting in an immunogenic tumor microenvironment. These events are highly desirable in the context of cancer immunotherapy (4,11).

Two aspects of oncolytic immunotherapy with poliovirus define its antineoplastic potential: receptor binding and translation of the viral genome. Its natural pathogenicity should be diverted to a therapeutic effect. The most important factor is the tropism by the target cells, necessary to provide the immune-activating and lytic viral load against the intended tumor target (9), since the concept of combating poliovirus cancer is largely based on this tropism by a molecule of the cell surface linked to the tumor cell, its stroma and tumor vascular proliferation (15).

The poliovirus recognizes a host cell receptor, which is sufficient to transmit vulnerability to the virus. CD155/PVR (the poliovirus receptor) is one of the main determinants of invasiveness and dissemination of glioblastoma in the central nervous system (16).

The virus must first contact its CD155 receptor which, in addition to poliovirus, serves as a ligand for the activation receptor DNAM-1 (CD226) expressed in natural killer (NK) cells, in CD8+ T cells and other immune cells (17). The CD155– DNAM-1 was implicated in the destruction of tumor cells mediated by NK cells (3,17).

Antigen presenting cells (APCs), such as macrophages and dendritic cells (CD), express CD155, making them susceptible to poliovirus infection, which leads to the release of pro-inflammatory cytokines. The segmentation of APCs associated with tumors by PVSRIPO can provoke pro-inflammatory stromal effects such as tumor-associated macrophages M1 (TAMs) (18) leading to the production of cytokines/chemokines interactions between the cells and the extracellular matrix (19). Due to the importance of TAMs in the tumor environment, repolarization towards a more pro-inflammatory and antineoplastic phenotype has been an attractive goal in cancer immunotherapy (9). Few events may be as competent in TAM repolarization as

viral infection. Thus, PVSRIPO leads to tumor regression mainly by the recruitment of an antineoplastic immune response (3,8).

The investigation of the innate immune response to PVSRIPO in xenotransplantation of mice with breast and prostate cancer indicated short-term viral persistence in infected tumors and significant tumor regression in both models. Nevertheless, tumor xenotransplantation models in nude athymic mice present a number of limitations that should be considered, given the absence of T cells and the unknown efficacy of human IFN in this environment (11).

Research by Brown *et al.* (2) on melanoma lines suggested that PVSRIPO deteriorate tumor cells effectively, released tumor antigens, and concomitantly induced the activation of DCs and macrophages. This generated specific immunity against the tumor antigen, and lytic damage to tumor cells, and this potential is based on the non-cytotoxic infection of APCs/DCs. PVSRIPO infection did not produce cytopathogenicity or cell death, but induced type I IFN responses, which stimulate antitumor immunity (2,20).

The most important first line defense of the host against virus infection is the innate antiviral response of IFNs. Type I IFNs are cytokines that stimulate antitumor immunity. Its production by the DCs after the encounter with the pathogen is fundamental for the regulation of the immune responses (2,20). Experiments suggest the existence of a process called cancer immuno-editing, where the system protects the host against oncogenesis and controls the development of tumors by eliminating malignant cells by the immune system, balancing and regulating genetically unstable tumor cells, and immune cells, and prevents the escape of variant neoplastic cells. Type I IFNs act in all of these stages because at least some types of cells produce it. Type I IFNs signal through an IFN alpha and beta receptor (IFNAR1), the alpha form being produced by leukocytes and the beta form by fibroblasts against a viral infection. They induce the infected cell itself to produce proteins that prevent virus replication (2,20).

PVSRIPO appears to be promising in accordance with phase I clinical trials performed at Duke University. Its intratumoral administration was performed in patients with recurrent glioblastoma, a treatment refractory cancer. The results demonstrated a 24-month overall survival of 24% in 24 patients treated with immunotherapy. Three patients remained alive 36 months after treatment (21).

PVSRIPO received the designation of innovative therapy by the Food and Drug Administration/Center for Biologics Evaluation and Research in May 2016, due to promising initial clinical results against glioblastoma (2,21).

Conclusions

In the future, the efficacy of oncolytic virus therapy is expected, with the onset of a variety of oncolytic viruses available and specific to each type and stage of cancer. Due to the heterogeneity of solid tumors, it is unlikely that all cancer cells within a tumor express CD155.

The first and most obvious of many challenges in creating safe and effective oncolytic viruses is to target cytotoxicity specifically for malignancy. Ongoing investigations focus on the relative contributions of PVSRIPO cytotoxicity to provide inflammatory cytotoxicity specifically for cancer cells, and on innate immune activation to the recruitment of effective immune responses.

Viruses can play a valuable role in future cancer immunotherapies. The innate antiviral response systems of the host present elaborate escape mechanisms and immune suppression adopted by viruses to deceive their hosts. In the promising scenario of immunotherapy against cancer, viral targeting strategies are likely needed to be combined with other therapeutic modalities.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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