Oncolytic Parvoviruses: An Emerging Frontier for Targeted Gene Therapy of Human Carcinoma

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Authors’ contributions

This work was carried out in collaboration between all authors. Author OIA designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors AKO, MKO and DJA managed the analyses of the study. Author OIA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Replication-competent oncolytic viruses (OVs) have been widely employed as vectors for cancer therapy because they selectively infect, replicate in and destroy tumor cells, while sparing their normal counterparts. Among OVs, the Rodent protoparvovirus 1 (RoPV) species within the Parvoviridae family deserves special consideration for its promising anticancer properties. Rodent inhabiting members such as the rat H-1PV virus attract high levels of interest as novel anticancer agents, because they can replicate autonomously in oncogene-transformed cells and exert both oncolytic effects in various cell cultures and animal models, while being non-pathogenic for humans. The H-1PV parvoviral capsid has been engineered to improve its affinity for pancreatic tumor cells; resulting in enhanced NK cell-mediated killing of pancreatic tumor cells. This review explains the
anticancer properties of oncolytic paroviruses, the bioethical issues associated with their use as therapeutic agents and the prospects of parovirus-based cancer immunotherapy to explore new prospects of treatments for human carcinoma.

Keywords: Oncolytic paroviruses; Parvoviridae; cancer immunotherapy; rodent protoparvovirus.

1. INTRODUCTION

The idea to use viruses as tools for cancer therapy arose as early as at the turn of the 20th century, when it was reported that leukemia patients who contracted influenza went into clinical remission [1-3]. These observations prompted intensive investigation of treatment strategies based on viruses with inherent antitumor activity, leading to the launch of the first clinical trials in the 1950s and 60s. Despite early promise, concerns regarding safety and a lack of efficacy caused a decline in oncolytic virotherapy research during the years that followed [4,5]. However, dramatic advances in the last two decades have given an understanding of molecular virology and the advent of genetic engineering with a resurgence of interest in the field of viral immunotherapy (for a review on the history of oncolytic virotherapy) [1,2,6].

Targeted gene therapy approaches are capable of introducing genes into cells in vivo without discrimination within target and non-target cells and cancer gene therapy has granted great hopes even though it is in its developmental trajectory [7,8]. Some domains of cancer gene therapy have been given greater attention, these include: suppression of cancer cells by introducing genes into tumor cells to lead cells toward apoptosis; inhibition of growth of cancer cells; enhancement of cancer cells chemo sensitivity; specific stimulation of the host’s immune response against the cancer cells by introducing the relevant genes into tumor cells [9].

In virotherapeutics, replication-competent oncolytic viruses (OVs) have been widely employed as vectors for cancer therapy because of their direct oncolytic effect via antitumor immune responses [10]. Virotherapeutics can be subdivided into two groups: replication-deficient virus vectors, which are used to deliver therapeutic genes to the target tumor, and replication-competent oncolytic viruses (OVs) [11]. More importantly, the balance between antitumor and antiviral immune reactions plays a major role in the efficiency of OV-mediated tumor suppression [12].

Among OVs, the Rodent protoparvovirus 1 (RoPV) species within the Parvoviridae family deserves special consideration for its promising anticancer properties [10]. The RoPV viruses exert striking oncosuppressive effects in various preclinical tumor models, kill tumor cells which resist conventional treatments, and have not been associated with disease in humans, laying the basis for the launch of the first phase III clinical trial using the rat oncolytic H-1 parovirus (H-1PV) [10,13].

2. ONCOlytic PARVOVIRUSES: PARVOVIRIDAE

Parvoviridae are small, non-enveloped, single-stranded DNA viruses that infect a wide variety of animal species, from insects to humans [9]. Rodent inhabiting members of the genus Parvovirus (PV), such as minute virus of mice (MVM) and rat H-1PV, attract high levels of interest as novel anticancer agents, because they can replicate autonomously in oncogene-transformed cells and exert both oncolytic and oncosuppressive activities in various cell culture and animal models, while being nonpathogenic for humans [14]. The Parvoviridae family presently includes 134 viruses that infect a broad range of hosts. They are characterized by anicosahedra capsid of about 25 nm in diameter containing a linear, single-stranded DNA molecule. The family is divided in two subfamilies, Parvovirinae and Densovirinae, members of which infect vertebrates and arthropods, respectively [15].

Eight genera have been classified as belonging to the Parvovirinae subfamily. The focus of the present review is on one of these genera, Protoparvovirus, and more particularly on one of its species, Rodent protoparvovirus 1 (RoPV1), whose members are able to replicate autonomously in close dependence on cellular S-phase factors [15]. RoPVs include the H-1 parovirus (H-1PV), the Kilham rat virus (KRV) and the Lu-III virus, the Mouse paroviruses (MPV) and the Minute viruses of mice (MVM). In unprotected fetuses and neonates of the natural or related hosts, RoPV infection can be pathogenic and even lethal, whilst in adults the
infection is clinically in-apparent though persistent [16]. Interestingly, these viruses are able to selectively replicate in cells of different origins, including human cells transformed by tumors [17].

The oncoseselectivity of PVs is due to efficient viral replication and toxicity in these cells [4]. Besides their anti-neoplastic activities, another advantage of rodent PVs for cancer therapy is the lack of previous exposure of humans to these agents, precluding the rapid elimination of the virus inoculums through preexisting antiviral immunity. These properties make these viruses very attractive candidates for use as anticancer agents [18].

3. ONCOLYTIC PROPERTIES OF THE H-1 PV PARVOVIRUS

H-1PV was recently shown to have induced pancreatic and colon carcinoma cells to display ligands to activating receptors of natural killer (NK) cells, resulting in enhanced NK cell-mediated killing of these cancer cells [19]. The immunostimulatory effect of RoPVs plays a significant role in their oncosuppressive activity. The occurrence of this immune component was evidenced by immunodepletion, immune-reconstitution and immunostimulation experiments [19]. Recently, H-1PV has been the subject of genetic manipulations that aimed at increasing virus oncospecificity and anticancer efficacy in order to optimize the therapeutic potential of RoPV-based treatments [5]. Genetic engineering of the H-1PV capsid proved to be a suitable approach to increase virus specificity for cancer cells at the level of cell recognition and entry [15]. Altogether, these results provide strong evidence that H-1PV treatment triggers an antitumor immune response contributing to the success of cancer virotherapy [10,20].

Allaume et al. [16] successfully engineered the rat H-1PV capsid to improve its affinity for tumor cells for greater oncosuppressive effects using the mice model. By analogy with the resolved crystal structure of the closely related parvovirus minute virus of mice, they developed a three-dimensional (3D) Insilico model of the H-1PV wild-type capsid [16]. Putative amino acids involved in cell membrane recognition and virus entry at the level of the 2-fold axis of symmetry of the capsid were identified within the dimple region [16]. They then engineered an entry-deficient viral capsid and inserted a cyclic RGD-4C peptide at the level of its 3-fold axis spike [16]. This peptide binds at αv β3 and αv β3 integrins, which are over expressed in cancer cells and growing blood vessels [16]. The insertion resulted in the efficient killing of pancreatic tumor cells by the re-engineered virus. This work has demonstrated that H-1PV can be genetically retargeted through the modification of its capsid, showing great promise for a more efficient use of this virus in cancer therapy [16].

4. H-1 PV PARVOVIRUS INDUCED APOPTOSIS OF CANCER CELLS

Rodent protoparvoviruses can destroy cancer cells through different mechanisms. Virus-induced apoptosis has been reported in several cell lines and is further supported by the fact that cellular regulators of both intrinsic and extrinsic apoptotic pathways are subjected to modulation upon parvovirus infection; as they initiate cell cycle arrest which leads to programmed cell death (apoptosis) and eventually, to cytolysis [21]. H-1PV has the ability to induce different cell death pathways in cancer cells, including necrosis, apoptosis, and lysosome-dependent cell death, while sparing non-transformed cells. Recently, the capacity of the virus to induce oxidative stress in cancer cells leading to DNA damage, cell cycle arrest, and apoptosis have been reported [22]. These effects are mediated by the nonstructural NS1 proteins on the parvoviral capsid. Although, the anticancer potential of H-1PV is supported by a large set of preclinical studies, its efficacy in clinical applications may be limited by the fact that PVs can still enter normal cells [19-22]. The uptake of the virus by non-tumor cells is expected to result in the sequestration of a significant portion of the administered viral dose away from the tumor target [8]. Targeting PVs (re-engineered Parvoviruses) enter into specific tumor cells, thus would increase the efficacy of PV-based treatments and provide additional safety against possible side effects on normal cells [3, 8, 16]. Furthermore, an ideal approach to increase the oncoselectivity of PVs would be to genetically redirect the binding of the virus to cancer cell-specific receptors as this has also proven successful in retargeting other non-enveloped viruses for gene therapy or virotherapeutics purposes. Further researches however, are still been done on attempts to retarget autonomous PVs in ways that can improve the delivery of targeted viruses into tumor cells [21-23].
5. LIMITATIONS OF PARVOVIRUS BASED GENE THERAPY OF CANCER

As promising as the H-1 PV parvovirus has proven to be in molecular medicine, one major limitation to improved viral delivery for effective oncolysis is in the genetic tropism of the viral capsids to specific human cancer cells that display tumor specific ligands [22-24]. Modification of genetic tropism in paroviruses generally consists of two steps; first, it is essential to abrogate the natural affinity of the virus to prevent it from entering cells that originally were competent for uptake. This is achievable by modifying the capsid residues involved in cell recognition and binding [25,24].

Secondly, it is necessary to retarget the virus specifically to cancer cells by grafting into the viral capsid a foreign peptide with high affinity for receptors that are exclusively or preferentially expressed on cancer cells [24]. This requires identification of an appropriate point within the viral capsid that will tolerate the insertion of the retargeting peptide, and the use of suitable ligand-peptides that, once inserted into the viral capsid, retain the affinity for their receptors [26,27]. Both steps are very challenging since the symmetry of the Parvoviral capsid is icosahedral in nature [27]. As a result, often times, changes in viral capsids are often incompatible with efficient particle formation and viral assemblage which eventually impedes the efficacy of the viral entry and oncolysis to be initiated by the targeted paroviruses [20,28].

Moreover, the steps involved in the retargeting of the H-1 PV also requires a precise knowledge of the capsid structural and functional elements and, in particular, of the region(s) involved in binding to one or several specific cell receptors none of which has been studied so far in the case of H-1PV [14,29].

6. BIOETHICAL CHALLENGES ASSOCIATED WITH VIRAL TARGETED GENE THERAPY

The completion of the human genome mapping made it possible to diagnose and treat many infectious diseases using targeted gene therapy; a frontier which led to the development of several studies with prospects for therapeutic use of viral genes for human infectious diseases [30,31]. However, these developmental strides have also triggered many bioethical controversies about the biosafety of genetic engineering and their use in eugenics [31-33]. Gene therapeutic strategy is characterized by transfer of genes for rearrangement of the genome of targeted cells to enable expression desired expression inserted genes or inhibition of specific genetic expressions in the host; as such, a notable methodology adopted overtly in gene therapy is the use of viral RNAi that have been widely used in biomedical research in recent years due to its relative ease of handling [31,34-36].

From a broader perspective of bioethical concern, the uses of viruses in genome therapy have been recently linked to many setbacks. Some of which are economic difficulties and wealth distribution, political and cultural conflicts of interest, scarce evaluation of the detrimental health impacts associated with the use of viruses in human therapy, as well as clinical dilemmas and legal issues respectively [31,36-38]. More importantly, targeted viral gene therapies are still novel procedures in different experimental stages and thus very risky therapies [36-38].

An overt ethical concern is the possibility of the oncolytic viral vectors known to be non-pathogenic which have encoding genes consisting RNAi to readily undergo genetic recombination and become more virulent or predisposing factors for new infections in humans [34,36,39]. Therefore, studies that evaluate the effects in experimental models and preclinical trials are needed in order to validate the potential effectiveness, risks and prospects of this type of therapeutic intervention for infectious human diseases [32-40].

7. CONCLUSION: FINAL NOTES AND PROJECTIONS OF VIRAL CANCER THERAPY

Although many scientific organizations have devoted different research funding into the possible effective cellular based therapy for Human carcinoma, several outcomes of laboratory research with animal models and human in-vivo evaluations have proven quite promising and an indication that further innovative topics of research should be explored in the targeted gene therapy of human cancer using viral vectors, most especially the oncolytic paroviruses. It is therefore, of great essence that oncolytic paroviral genomes be further studied for better molecular modifications that will result in perfect oncospecific cytolysis of human metastatic cancer stem cell forms. This will lay scientific bedrock for the therapy of metastatic
cancer stem cell forms that have defied conventional radio therapeutic and chemotherapeutic methods.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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