Vaccine 31 (2013) 4252–4258

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Oncolytic myxoma virus: The path to clinic

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ARTICLE INFO

Article history:
Received 23 February 2013
Accepted 13 May 2013
Available online 29 May 2013

Keywords:
Myxoma virus
Oncolytic virotherapy
Hematological malignancies
Pancreatic cancer

ABSTRACT

Many common neoplasms are still noncurative with current standards of cancer therapy. More therapeutic modalities need to be developed to significantly prolong the lives of patients and eventually cure a wider spectrum of cancers. Oncolytic virotherapy is one of the promising new additions to clinical cancer therapeutics. Successful oncolytic virotherapy in the clinic will be those strategies that best combine tumor cell oncolysis with enhanced immune responses against tumor antigens. The current candidate oncolytic viruses all share the common property that they are relatively nonpathogenic to humans, yet they have the ability to replicate selectively in human cancer cells and induce cancer regression by direct oncolysis and/or induction of improved anti-tumor immune responses. Many candidate oncolytic viruses are in various stages of clinical and preclinical development. One such preclinical candidate is myxoma virus (MYXV), a member of the *Poxviridae* family that, in its natural setting, exhibits a very restricted host range and is only pathogenic to European rabbits. Despite its narrow host range in nature, MYXV has been shown to productively infect various classes of human cancer cells. Several preclinical *in vivo* modeling studies have demonstrated that MYXV is an attractive and safe candidate oncolytic virus, and hence, MYXV is currently being developed as a potential therapeutic for several cancers, such as pancreatic cancer, glioblastoma, ovarian cancer, melanoma, and hematologic malignancies. This review highlights the preclinical cancer models that have shown the most promise for translation of MYXV into human clinical trials.

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1. Introduction

Cancer remains a major public health problem worldwide. For example, one out of four deaths in the United States is due to cancer [1]. Current standards of cancer therapy include resection surgery (if applicable), radiation, chemotherapy, immunotherapy, and/or biological therapy. However, available treatments for many common cancers remain noncurative and in many cases prolong survival rates only in the short term. Therefore, development of more efficacious treatments is much needed in order to significantly prolong the lives of cancer patients and eventually cure a wider spectrum of cancers. One of the newer and promising cancer therapeutic strategies is oncolytic virotherapy, and the first candidate viruses are rapidly approaching licensure in North America and Europe [2]. Successful oncolytic virotherapy in the clinic will possess two closely inter-related properties: the ability to destroy cancer cells directly but also the capacity to enhance acquired immune responses against tumor antigens, *i.e.*, oncolytic virotherapy and anti-tumor immunostimulation are inextricably linked to each other. In general terms, a replication-competent virus, which spares normal tissues but selectively replicates in cancer cells, is used to specifically infect and eliminate cancerous tissues [3]. Viruses with demonstrated oncolytic potential include numerous candidates that are relatively nonpathogenic to humans but have a biologic proclivity to replicate selectively in human cancer cells. Examples of viruses that are in various stages of clinical and preclinical development include measles virus, vesicular stomatitis virus, adenovirus, reovirus, herpes simplex virus and two poxviruses, vaccinia virus and myxoma virus (MYXV) (reviewed in [4–9]). Vaccinia virus, a prototypic member of the *Poxviridae* family, has been widely developed as a vaccination platform, and more recently is being tested as an oncolytic virotherapeutic in Phase II clinical trials for various late stage cancers, including liver cancer and malignancies that metastasize to the liver [4,10–14]. Vaccinia virus, long used in the worldwide vaccination program against smallpox, is of unknown origin in terms of its evolutionary host, but has been tested extensively in humans.

In general, poxviruses infect a wide range of hosts including humans, monkeys, mice, rabbits and insects, but individual members can be highly species-specific in terms of the hosts that they can infect [15,16]. For example, vaccinia virus infects a wide variety of vertebrate hosts whereas MYXV is completely restricted to

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0264-410X/$ – see front matter. Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.vaccine.2013.05.056

Table 1
Summary of the oncolytic potential of MYXV tested in preclinical animal models of cancer.

Type of cancer	Animal model	Tumor establishment	MYXV administration	Outcome (references)
Acute myeloid leukemia (AML)	NSG	Human AML cells in bone marrow xenograft	*Ex vivo*[a]	90% of mice free of human AML cells in BM [40]
Multiple myeloma (MM)	NSG	Human MM cells in bone marrow xenograft	*Ex vivo*[a]	100% of mice free of human MM cells in BM [44]
Pancreatic cancer	NOD/SCID	Human pancreatic cancer cells in intraperitoneal cavity	Intraperitoneal	Reduced tumor burden and prolonged survival [51]
	C57BL/6	Murine pancreatic cancer cells in intraperiotoneal cavity	Intraperitoneal	100% survival when combined with gemcitabine [51]
Glioma	CD-1 nude	Human gliomas in mouse brain	Intratumoral	92% of mice cleared of tumors and cured [66]
	Fischer 344 rats	Racine gliomas in rat brain	Intratumoral	Prolonged survival when combined with Rapamycin [29]
Rhabdoid tumors	CD-1 nude	Human rhabdoid tumor cells in mouse brain	Intratumoral	Reduced tumor mass; 66.7% of mice had long-term survival [71]
		Human rhabdoid tumor cells in hind flank of mice	Intratumoral	Reduced tumor mass [71]
Medulloblastoma	CD-1 nude	Human medulloblastoma in mouse brain	Intratumoral	Prolonged survival; 60% of mice had long-term survival when combined with rapamycin [72]
Melanoma	C57BL/6	Subcutaneous murine melanoma	Intratumoral	Reduced tumor mass [81]
			Intravenous	Decreased development of lung metastasis [81]
	C57BL/6	Murine melanoma	*Ex vivo*[a]	Prevented tumor implantation [81]

[a] *Ex vivo* treatment of samples with MYXV prior to implantation/engraftment.

lagomorphs and is only pathogenic in the European rabbit [17–19]. MYXV is the prototypic member of the *Leporipoxvirus* genus within the *Poxviridae* family [20–22]. The MYXV Lausanne strain genome is 161.8 kbp in size, encoding about 171 genes [23]. The central region of the genome encodes less than 100 genes that are highly conserved in all poxviruses while the terminal genomic regions are enriched for more unique genes that encode immunomodulatory and host-interactive factors that are involved in subverting the host immune system and other anti-viral responses [20,24–26]. A more detailed background on MYXV and its history has been described in recent reviews [21,27].

MYXV causes a lethal disease called myxomatosis in European rabbits (*Oryctolagus cuniculus*) but the virus actually co-evolved within lagomorphs of the *Sylvilagus* genus, such as the Brazilian tapeti [21,28]. In the tapeti, MYXV replicates robustly and transmits efficiently from host-to-host but causes no overt disease [28]. The basis for the extreme virulence of MYXV in the European rabbit, and absence of pathogenesis in the tapeti, is not well understood but the virus is essentially nonpathogenic for any host outside the lagomorph family [17–19,21]. Indeed, the virus fails to replicate to any appreciable extent in any non-rabbit host tested to date, including highly immunodeficient mice [21,29]. MYXV can successfully replicate in rabbits due to the ability of MYXV to escape multiple diverse host innate and adaptive immune responses [20,22,25,26]. Despite its narrow host range in nature, MYXV has been shown to productively infect various classes of human cancer cells due to several factors, including: (I) the failure of most cancer cells to induce appropriate anti-viral responses, such as the synergistic interferon and tumor necrosis factor pathways that efficiently aborts MYXV replication in normal primary human cells [30,31] and (II) the constitutive activation of intracellular pathways related to cellular transformation, such as the phosphorylation of Akt, commonly found in many human cancer cells [32]. A detailed study has shown that MYXV-encoded ankyrin-repeat host range factor, M-T5, interacts with Akt and this interaction is required for the enhanced phosphorylation of Akt [32,33]. Pharmacologic manipulation of Akt activation affects MYXV tropism, indicating a direct correlation between endogenous activated signal transduction pathways and the permissiveness of MYXV to target human cancer cells [34]. Additionally, our laboratory has demonstrated an important role for the IFN signaling in the permissiveness of MYXV to certain specific cell types [35]. Co-treatment of primary human fibroblasts with type I IFN and TNF induces a synergistic antiviral state that aborts MYXV infection [31]. Importantly, a wide spectrum of human cancer cells has been shown to unable to induce the synergistic antiviral state, which may allow for selective/productive MYXV infection in a wide variety of human cancer cells [30].

Attractive features of MYXV as an oncolytic agent include its ability to productively infect various human cancer cells and its consistent safety in all non-rabbit hosts tested, including mice and humans [17–19,21,36]. The work from our laboratory and of others clearly demonstrates that MYXV is an attractive candidate oncolytic virus (reviewed in [22,37,38]), and hence, MYXV is currently being developed as a candidate therapeutic for several cancers, including ovarian cancer, glioblastoma, myeloid leukemia, multiple myeloma (MM), melanoma, and pancreatic cancer. This review updates the current status in the oncolytic potential of MYXV for the treatment of these cancers in preclinical animal models (Table 1) and highlights the projected path toward human clinical trials with this virus.

2. Hematological malignancies: acute myeloid leukemia and multiple myeloma

Hematological malignancies under consideration here include acute myeloid leukemia (AML) and multiple myeloma (MM) that mainly affect adults. Approximately 10% of Americans diagnosed with cancer each year will have one of these blood cancers (National Cancer Institute, Surveillance Epidemiology, and End Results). For high-risk patients with AML, either autologous or allogenic hematopoietic stem cell transplantation has been used to rescue immune function following myeloablative therapy with high dosages of chemotherapeutics. Autologous stem cell transplants are safer than allogeneic transplants but suffer the downside of being potentially contaminated with residual cancer cells from the donor that can potentially re-seed the cancer following engraftment. Various purging strategies have been attempted in the past to selectively kill off cancer cells in contaminated autologous