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Review

Oncolytic virotherapy of gynecologic malignancies

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ABSTRACT

Objective. Gynecologic cancer is still the third leading cause of cancer death among women in the US. Therapeutics employing novel mechanisms of action are therefore urgently needed. Oncolytic viruses (OVs) selectively infecting and replicating in cancer cells have recently attracted considerable interest as promising anti-cancer agents. Here, we provide an overview of different OVs currently being used for virotherapy of gynecologic cancers and discuss challenges and implications for their future development.

Methods. Relevant literature obtained from the PubMed database by searching for articles including the terms "oncolytic" or "virus", or "virotherapy" as well as "ovarian" or "cervical" was thoroughly reviewed.

Results. Preclinical *in vivo* models as well as early clinical trials demonstrated safety and efficacy when targeting gynecologic malignancies with OVs.

Conclusions. While gaining more and more insight into the underlying molecular mechanisms of OVs, virotherapy represents an appealing approach to fight gynecologic malignancies.

Contents

Introduction

In 2009, about 80,000 new cases of gynecologic cancers were diagnosed in the US [1]. The most common malignancy of the female genital tract is endometrial cancer. Since curative surgery is possible, adjuvant therapy is necessary only in patients at high risk of recurrence [2]. Cervical carcinoma is reliably detected by both non-invasive methods and HPV typing even in non-invasive stages. As a consequence, its incidence is decreasing in developed countries. However, it remains the second most common type of malignant tumors among women worldwide, and patients with recurrent or metastatic disease often have a poor prognosis. In fact, most deaths occur from ovarian cancer. Because of its vague symptoms, approximately 65% of all cases are diagnosed at late stages III or IV. Despite

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Table 1
Characteristics of viral species used for virotherapy.

Virus families and oncolytic viruses		Genome	Clinical features of human wild-type infections
Adenoviridae	Adenovirus	DNA (double-stranded), 30–40 kb	Respiratory diseases, gastroenteritis, cerato-conjunctivitis, hemorrhagic cystitis, hepatitis, myocarditis
Poxviridae	Vaccina virus	DNA (double-stranded), 300–400 kb	None
Herpesviridae	HSV-1, HSV-2	DNA (double-stranded), 150–200 kb	Herpes labialis, oropharyngeal herpes, herpes genitalis, encephalitis, ceratitis
Parvoviridae	H-1, minute virus of mice	DNA (single-stranded), 5 kb	None
Picornaviridae	Coxsackievirus Echovirus	RNA (single-stranded, non-segmented), 7–8 kb	Flu-like illness, diarrhea, meningitis, encephalitis, pericarditis
Paramyxoviridae	Measles virus (vaccine strains) Newcastle disease virus Mumps virus (vaccine strains)	RNA (single-stranded, non-segmented), 100–300 kb	None
Togavirida	Sindbis virus	RNA (single-stranded, non-segmented), 11 kb	Rash, arthritis
Rhabdoviridae	Vesicular stomatitis virus	RNA (single-stranded, non-segmented), 11 kb	Conjunctivits, flu-like illness
Reoviridae	Reovirus	RNA (double stranded, 10 segments), 60–80 kb	None

advanced surgical techniques and modern chemotherapy, the prognosis has not changed over the last two decades and the 5-year survival rate remains as low as 20–30% [3]. In 2009, about 28,000 women died of gynecologic cancer, making this group of disease the third leading cause of cancer death among women in the US. [1]. Therefore, new therapeutics with novel mechanisms of action and without cross-resistances to currently available treatments are urgently needed.

Since early case studies described tumor regression following naturally acquired virus infections [4,5], oncolytic viruses (OVs) that selectively infect or replicate in cancer cells attracted considerable interest as promising anti-cancer agents (Table 1). In contrast to classical gene therapy, where *replication-incompetent* viral vectors are used for therapeutic gene delivery, OVs are *replication-competent* agents that selectively kill cancer cells while sparing normal cells (Fig. 1). Infection with OVs leads to the release of progeny virions that can spread throughout the tumor, whereas conventional viral vectors do not spread and are thus unable to transfer their therapeutic gene into the majority of tumor cells. Beyond the direct cytopathic effect achieved by viral replication (i.e., oncolysis), OVs can deliver therapeutic transgenes to enhance their antineoplastic properties.

The first reports to utilize replicating viruses for gynecologic cancer treatment date back a century. In 1912, a woman with cervical carcinoma responded to repeated rabies vaccinations [6]. An early clinical trial involving gynecologic malignancies was performed in the 1950s when 30 patients with cervical cancer were treated with different adenovirus serotypes. More than 50% of patients had a "marked to moderate local tumor response", with areas of necrosis confined to the cancerous tissue. However, no systemic responses were reported, and survival was not significantly prolonged [7]. In 1965, intratumoral treatment of a woman suffering from cervical cancer with Newcastle disease virus induced shrinkage of local tumor mass and a supraclavicular lymph node metastasis [8]. In 1988, Shimizu et al. vaccinated gynecologic cancers patients with mumps virus followed by local or systemic viral administration. In five of seven patients with ascites or pleural effusion, intracavitary injection resulted in complete clinical resolution [9].

These early clinical trials were performed with wild-type and therefore non-engineered *in vitro*-passaged virus strains (first generation OVs). Due to advances in biotechnology, the field of virotherapy has rapidly evolved over the past two decades and innovative recombinant selectivity-enhanced viruses (second generation OVs) as well as therapeutic transgene-delivering "armed" oncolytic viruses (third generation OVs) have been engineered. Today, hundreds of patients are being treated on prospectively designed clinical trials (including phase III) (reviewed in Ref. [10]).

This review of oncolytic virotherapy focuses on the treatment of gynecologic malignancies. The PubMed database was searched for articles including the terms "oncolytic" or "virus" or "virotherapy", as well as "ovarian" or "cervical". The abstracts of retrieved citations were reviewed and prioritized. Full articles were obtained, and references were checked for additional material when appropriate. The data were summarized to provide an overview of different OVs used for virotherapy of gynecologic cancers. This includes targeting strategies to enhance tumor selectivity, the use of therapeutic-gene-carrying OVs to increase oncolytic properties, methods for non-

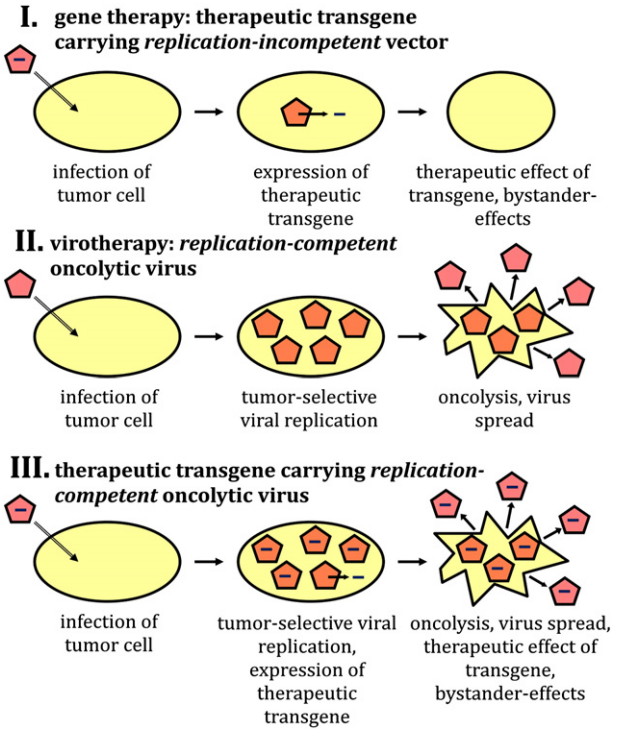

Fig. 1. From gene therapy to virotherapy. (I) Classical gene therapy: non-replicating gene therapy vectors are used for therapeutic gene delivery in tumor cells. Their therapeutic effect is restricted to the initially infected cells and may be enhanced by bystander effects that harm surrounding cells. (II) Virotherapy: replication-competent oncolytic viruses specifically target tumor cells. While sparing normal cells, the infection of malignant cells leads to cell killing and the release of progeny virions that can spread further throughout the tumor. (III) Therapeutic transgene carrying oncolytic virus: to further enhance cancer cell killing, replication-competent oncolytic viruses can be "armed" with therapeutic genes that generate therapeutic proteins, which also spread throughout the tumor.