Mini-review

Adeno-associated virus-mediated cancer gene therapy: Current status

Jingfeng Luo a, Yuxuan Luo b, Jihong Sun a, Yurong Zhou a, Yajing Zhang a, Xiaoming Yang a,c,∗

a Department of Radiology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Qingchun Road NO.3, Hangzhou, Zhejiang, China
b Department of Nephrology, Zhuji People’s Hospital, Zhuji, Zhejiang, China
c Image-Guided Bio-Molecular Intervention Research, Department of Radiology, University of Washington School of Medicine, Seattle, WA, USA

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ABSTRACT

Gene therapy is one of the frontiers of modern medicine. Adeno-associated virus (AAV)-mediated gene therapy is becoming a promising approach to treat a variety of diseases and cancers. AAV-mediated cancer gene therapies have rapidly advanced due to their superiority to other gene-carrying vectors, such as the lack of pathogenicity, the ability to transflect both dividing and non-dividing cells, low host immune response, and long-term expression. This article reviews and provides up to date knowledge on AAV-mediated cancer gene therapy.

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Introduction

Cancer is still one of the most devastating diseases in the world. According to the Centers for Disease Control and Prevention (CDC), cancer incidence in the U.S.A. was 7,178,172 from 2006 to 2010, with mortality reaching 2,830,559 (http://www.cdc.gov/cancer/dcpc/data/). The existing therapeutic approaches, such as surgery, thermotherapy, chemotherapy, and radiotherapy, often have severe side effects, such as cytotoxicity to normal cells and strong host immune responses. Most critically, some cancers barely respond to these therapies [1,2] and so alternative therapeutic approaches are needed. Gene therapy is one such attempt.

Gene therapy consists of three basic steps: (i) constructing a gene-carrying vector, (ii) transferring genes into target cancer cells with the vector, and (iii) expressing gene products to kill cancer cells. Constructing an effective vector for carrying therapeutic genes is essential for successful gene therapy. Gene-carrying vectors can be divided into two categories: non-viral vectors and viral vectors. Non-viral vectors, such as naked plasmids, microbubbles, nanoparticles, liposomes, and polymers, are safe, low-cost, and offer large insert size of genes; however, in vivo gene transfection and expression is inefficient and transient, despite low immunogenicity [3]. Viral vectors, such as adenoviral vectors, retroviral vectors, and lentiviral vectors, provide effective gene transduction and expression; however, they have several disadvantages, including high immunorejection, possible tumorigenicity, uncertain insertional mutagenesis, and limited constructive sizes for gene insertion. These disadvantages have prevented translation into clinical practice.

Thus, it is imperative that gene-carrying vectors have (1) high transferring ability, (2) low immunorejection, and (3) long-term gene expression [4]. Adeno-associated virus (AAV) gene-carrying vectors meet these requirements.

AAVs for cancer gene therapy are superior to other gene vectors, with relatively low host immune response, weak toxicity, and long-term gene expression. AAVs have been successfully used to deliver and transfer a variety of therapeutic genes to cancer cells, including suicide genes, anti-angiogenic genes, and immune-related genes, to inhibit tumor initiation, growth, and metastasis. Herein, we review the development and recent advances of AAV-mediated cancer gene therapy, aiming to provide up-to-date information on the clinical application of AAV-based gene therapy.

Biology of AAVs

The adeno-associated virus, first discovered in the 1960s [5], is replication-deficient and belongs to the family of Parvoviridae. As the best known representative of all the AAVs, AAV2 contains a single stranded DNA genome comprising inverted terminal repeats (ITRs) and two open reading frames encoding replication and capsid proteins. The structure of AAV2 has been determined to 3-Å resolution (Fig. 1) [7]. Recently Gao et al. have obtained more than 120 novel primate AAVs [8]. The diverse tissue and cell tropisms of mainly used AAV vectors were listed in Table 1.

Advances of AAV vectors

The AAV based gene delivery systems are more attractive compared to other vectors. More benefits were discovered using AAV vectors such as more safety due to the lack of pathogenicity, more
varied host and cell-type tropisms, long-term gene expression, ability to transfect both dividing and nondividing cells, absence of enormous immune response. Furthermore, the discovery of more novel AAV serotypes will further extend the scope of application of an AAV based gene delivery system.

However several problems about this gene delivery system should be addressed. Firstly, the effective packaging capacity of AAV is limited to 4.1–4.9 kb [27], which restricts the transduction of larger genes. Secondly, antibody neutralization rises because of prior exposure of human beings with multiple AAV serotypes [28]. Thirdly, challenges with high-efficient transduction to specific cell populations remain in an AAV mediated gene delivery system. Since these problems influenced the extended application of AAV based gene therapy, a variety of attempts to improve this vector have been carried out. Self-complementary AAV (scAAV) vectors can fold into double-stranded DNA (dsDNA) without DNA synthesis or base-pairing between multiple vector genomes [29] bypassing the conversion to dsDNA. Naturally, these vectors are more sufficient to transgene expression than normal AAV vectors. The clinical application of AAV vector was slowed down due to the limitation of the packaging capacity of rAAV. Cotransduction of dual AAV vectors seems to be an alternative to solve this problem. Transgene expression cassettes are split into two, and each is packaged into an AAV vector. Then expression of full-length transgene is obtained via homologous recombination or viral inverted terminal repeat mediated recombination. Since low levels of pre-existing neutralizing antibodies significantly reduced the efficacy of therapeutic AAV gene delivery, modification of AAV capsid involved in interactions with host immunity has been a good idea to escape neutralization. Directed selection of AAV variants, “shielding” polymers, site-directed mutagenesis and directed evolution of AAV capsid made the neutralization escape of AAV based delivery system feasible [30].

Table 1
The different tissue and cell tropisms of mainly used AAV serotypes.

<table>
<thead>
<tr>
<th>Serotypes</th>
<th>Origins</th>
<th>Tropisms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAV1</td>
<td>Simian sources</td>
<td>Skeletal muscle, spinal cord, heart</td>
<td>[9,10]</td>
</tr>
<tr>
<td>AAV2</td>
<td>Human clinical specimens</td>
<td>CNS, retina, ubiquitous</td>
<td>[11–13]</td>
</tr>
<tr>
<td>AAV3</td>
<td>Human clinical specimens</td>
<td>Cochlear inner hair cells, liver cancer cells</td>
<td>[14,15]</td>
</tr>
<tr>
<td>AAV4</td>
<td>Simian sources</td>
<td>Heart, lung</td>
<td>[16]</td>
</tr>
<tr>
<td>AAV5</td>
<td>Human clinical specimens</td>
<td>Apical airway cells, liver cells</td>
<td>[17]</td>
</tr>
<tr>
<td>AAV6</td>
<td>Recombinant of AAV2(5′) and AAV1(3′)</td>
<td>Apical airway cells</td>
<td>[18]</td>
</tr>
<tr>
<td>AAV7</td>
<td>Rhesus monkey</td>
<td>Retina, muscle, liver</td>
<td>[19]</td>
</tr>
<tr>
<td>AAV8</td>
<td>Rhesus monkey</td>
<td>Skeletal and cardiac muscles, retina</td>
<td>[20,21]</td>
</tr>
<tr>
<td>AAV8.h.8</td>
<td>Rhesus monkey</td>
<td>Muscle, liver</td>
<td>[8]</td>
</tr>
<tr>
<td>AAV9</td>
<td>Human sources</td>
<td>CNS, peripheral tissues,</td>
<td>[8,22]</td>
</tr>
<tr>
<td>AAV10</td>
<td>Cynomolgus monkeys</td>
<td>Mouse heart, lung, liver, kidney, and uterus</td>
<td>[23]</td>
</tr>
<tr>
<td>AAV10.h.10</td>
<td>Rhesus macaque</td>
<td>CNS</td>
<td>[24]</td>
</tr>
<tr>
<td>AAV11</td>
<td>Cynomolgus monkeys</td>
<td>Mouse muscles, kidney, spleen, lung, heart, and stomach</td>
<td>[23]</td>
</tr>
<tr>
<td>AAV12</td>
<td>Simian sources</td>
<td>Muscle and salivary glands</td>
<td>[25]</td>
</tr>
<tr>
<td>AAV12.h.43</td>
<td>Rhesus monkey</td>
<td>CNS</td>
<td>[26]</td>
</tr>
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</table>

Fig. 1. Structure of the AAV-2 subunit and comparison with related structures. (a) Experimental electron density for AAV-2. Phases for this 3-Å resolution electron density map are independent of the AAV-2 model, having been obtained by symmetry averaging and extension from a CPV model at 15-Å resolution. Density is clear and allows an unambiguous fitting of the chemical sequence throughout VP1. (b) Ribbon drawing of the AAV-2 subunit. The locations of the neighboring symmetry axes are shown. The β-barrel is on the inner surface of the capsid (pink) with strands of the two sheets labeled conventionally as A, B, I, D, and G, and C, H, E, and F. Loops are labeled according to the flanking strands – e.g., GH loop. Regions where the sequence differs greatest between the AAV serotypes are colored purple [6]. (c) Comparison of the backbones of AAV-2 (red) and canine parvovirus (cyan). The loop structure, which is responsible for many of the viral–host interactions, differs substantially between AAV-2 and canine parvovirus, and is largely absent from insect densoviruses (not shown). Reprinted with permission from Ref. [7]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Development of AAV-mediated gene therapy

A variety of preclinical experiments involving AAV-based gene therapies have been carried out. In 1984, a study reported the first construction of AAVs as vectors for gene transfer to eukaryotic cells [31], while the urgency of curing cystic fibrosis (CF) motivated the development of in vivo AAV-based gene therapy technology. By utilizing AAV vectors, scientists successfully transduced a therapeutic gene, cystic fibrosis transmembrane regulator (CFTR), into the airways of rabbits and monkeys. Expression of CFTR was detected for as long as 6 years in the airways. Subsequently, the first trial of AAV-mediated CF gene therapy was reported in 1995 [32]. Since then, extensive research has been done on tissue tropism, targeting cell receptors associated with infection, gene/vector delivery routes, pathophysiologic effects, and AAV vector immune profiling. The first licensed gene therapy product with an AAV vector was Glybera, specifically designed and used to supplement deficiency in lipoprotein lipase (LPL). In recent years, gene therapies with different subtypes of AAV vectors have been reported for treatments of a variety of diseases as listed in Table 2.

Advances in AAV-mediated cancer gene therapy

AAV-mediated suicide gene therapy

Suicide gene therapy, also called gene-directed enzyme prodrug therapy (GDEPT) or molecular chemotherapy, is currently the most promising strategy for genetic treatment of different cancers. GDEPT relies on the intratumor delivery of a transgene encoding an enzyme, which then activates a systemically-delivered prodrug that inhibits DNA polymerase and blocks DNA replication in tumor cells. Among the candidate genes, the herpes simplex virus thymidine kinase gene/ganciclovir prodrug (HSV-tk/GCV) system is an excellent example of the clinical application of GDEPT (Fig. 2) [58]. Studies have shown that the AAV-mediated HSV-tk/GCV therapeutic system generates strong antitumor efficacy [59,60].

One of the most attractive elements of the HSV-tk/GCV therapeutic system is its bystander effect, i.e., the killing of untransduced tumor cells surrounding transduced tumor cells [61]. This phenomenon is mainly caused by the free passive diffusion of antimetabolites or transfer of phosphorylated GCV molecules between cells via gap junction intercellular communication (GJIC) [62]. Connexin is an important GJIC molecule generally expressed in the cytosol. Some study groups have demonstrated that overexpression of connexin43 restored GJIC in tumor cells and thereby resulted in the increased antitumor effect of the HSV-tk/GCV system [63,64]. Recently, a novel family of GJIC named Pannexin (Panx) [65] may play the same roles as the connexins [66].

AAV-mediated antiangiogenesis gene therapy

Angiogenesis often accompanies the growth of tumors to provide oxygen and nutrients, causing rapid proliferation of cancer cells. Antiangiogenic therapy was developed to starve tumor cells [67]. Vascular endothelial growth factor (VEGF), an important mediator of angiogenesis in both healthy and diseased tissues, is a crucial antitumor target. A study demonstrated that a single intravenous administration of AAV/VEGF-Trap led to long-term efficacy and permitted not only suppression of primary tumor growth but also prevention of pulmonary metastasis [68]. AAV-mediated transduction of other antiangiogenic genes, such as pigment epithelium-derived factor (PEDF) [69,70], endostatin 34, Kringle 5 [71], and kallistatin [72], also showed significant inhibition of tumor angiogenesis, tumor growth, and metastasis. Overexpression of the specific antagonist of hepatocyte growth factor (HGF) NK4, consisting of an N-terminal hairpin domain and four kringle domains, can antagonize the HGF/c-Met system competitively, inhibit c-Met signaling and tumor metastasis, and therefore offer additional antiangiogenic activity [73].

AAV-mediated immune gene therapy

Immune gene therapy has advanced rapidly over the past decades and is becoming an important approach in the treatment of different cancers. AAV-mediated immune gene therapy is based on the successful activation of the host immune system upon transfer of therapeutic genes to targets cells, including cytokines, immunogenic cell surface molecules, and tumor antigens, as listed in Table 3.

Other AAV-mediated gene therapies

The negative signaling associated with programmed death-1 (PD-1) contributes to tumor evasion. Investigators delivered the extracellular domain of murine PD-1 to a tumor site using AAV vectors and obtained high antitumor efficacy [84]. Since the Fas/Fas ligand (FasL) system involves apoptosis of tumor cells, AAV-mediated transduction of human Fasl genes in human laryngeal carcinoma Hep II) recombinant polypeptide of human fibronectin suppresses the growth and spontaneous metastasis of breast carcinoma, and prolongs the survival of tumor-bearing mice [86]. Prostate apoptosis response-4 (Par-4) is the tumor-suppressor protein that results in cell apoptosis in tumor cells not in normal cells. A study showed...
that expression of AAV/Par-4 induced rapid cell death in the HepG2 hepatocarcinoma model [87].

AAV3-mediated expression of the pyruvate dehydrogenase E1 alpha subunit gene can also result in the apoptosis of liver cancer cells [15]. Tumor necrosis factor (TNF) related apoptosis-inducing ligand (TRAIL) receptor 2 (also called death receptor 5, DR5) is usually expressed in tumor cell lines but not in normal cells. Investigators have demonstrated that an AAV-based anti-DR5 mouse-human chimeric antibody can markedly inhibit tumor growth in vitro and in vivo [88]. Survivin is an apoptosis protein. The binding of heat shock protein 90 (Hsp90) to survivin can inhibit the degradation of survivin by the ubiquitin-proteasome system. Since survivin Lys-79~Leu-87 is the binding site for Hsp90, the identical 9-amino acid peptide, named shepherdin, was constructed. AAV-mediated NT4-Ant-shepherdin, consisting of a cell-penetrating peptide (Ant), the signal peptide of neurotrophin-4 (NT4) and shepherdin, can significantly suppress the growth of the lung cancer cell line A549 by inducing apoptosis [89]. Telomerase is made of the catalytic subunit of human telomerase reverse transcriptase (hTERT) and telomerase RNA (hTR). Overexpression of a 27 kDa C-terminal polypeptide of hTERT (hTERTC27) carried by recombinant AAV can prevent the growth of human U87-MG glioblastoma cells in nude mice by increasing necrosis, apoptosis and neutrophil infiltration, and by decreasing microvascular density [90].

**AAV-mediated RNA interference therapy**

RNA interference (RNAi) is a therapeutic biological tool in different cancers. Several types of non-encoding RNAs (siRNAs, shRNAs, and artificial microRNAs) have been used in preclinical studies through the endogenous RNAi pathway. AAV-mediated short hairpin RNA (shRNA) is ubiquitously used in gene knockdown applications. Androgen receptor (AR) is associated with prostate cancer progression. Transduction of AAV/shRNA against AR inhibits the growth of tumors, even abrogating xenograft tumors within 10 days. Furthermore, a study demonstrated that efficacy was achieved by reducing the expression of AR-related survival genes, leading to a dramatic apoptotic response [91].

MicroRNA (miRNA) is a type of highly conserved small RNA molecule that plays an important role in the regulation of gene expression. Systemic administration of AAV-mediated miRNA-26a led to the inhibition of cancer growth, induction of tumor apoptosis, and protection from disease progression [92]. Participation of miRNA in the pathophysiology of pancreatic cancers was also reported [93]. Knockdown of Four and a half (LIM) protein 2 (FHL2) with AAV-mediated FHL2 shRNA transduction in colon cancer resulted in G0/G1 cell cycle arrest and inhibition of tumor cell growth. Delivery of scAAV2-based siRNA against the unfolded protein response inositol-requiring protein 1α (IRE1α), X-box-binding protein...
Fig. 3. Effect of antiangiogenic gene therapy and paclitaxel on metastasis of orthotopically transplanted human breast cancer cells (intervention model). MDA-MB-231-luc cells were transplanted into mammary fat pads of female, athymic mice. Whole body images were obtained on a weekly basis after intraperitoneal administration of luciferin in a Xenogen system (a). Luminescence signals from the primary tumors were too strong and were overlapping with the signals originating from the metastatic sites. Therefore, the primary tumors were shielded (lower half) to reveal tumor metastasis to lungs and lymph nodes (days 21 and 42). Intensity of signals is shown at the bottom. On day 42, mice were killed and brachial lymph nodes and lung tissues were removed for ex vivo imaging. (c) Adeno-associated virus (AAV)-LacZ; E, AAV-P125A-endostatin; T, paclitaxel; T + E, combination treatment; LN, lymph node. Panel (b) shows relative luciferase-positive pixels from the metastatic sites. Each value is a mean of five animals ± s.d. Panel (c) shows the histopathology of lungs. The lung tissues were stained with hematoxylin and eosin stain and the black arrow shows the tumor that has metastasized to the lungs (×200). **Denotes statistical significance (P < 0.02). Reprinted with permission from Ref. [106].
1(XBP)-1, and activating transcription factor 6 (ATF6) remarkably suppresses breast tumor angiogenesis [94]. Snail is an important transcriptional factor involved in the antiapoptotic and chemoresistant phenotype of pancreatic cancer. Administration of AAV-mediated snail siRNA inhibits the growth of xenografted pancreatic cancers [95].

**AAV-mediated targeting gene therapy**

To date, the primary weakness of systemic delivery of AAV-based therapeutic genes is low tumor-targeting efficiency. Specificity may be improved by adding tumor-specific promoters to AAV vectors. To date, there are a variety of AAV-mediated therapeutic genes driven by various tumor-specific promoters, such as human telomerase reverse transcriptase (hTERT) [96–98], extracellular domain of tumor necrosis factor-related apoptosis-inducing ligand (sTRAIL) [99], tumor-targeting motif, including RGD, and tenasin C (TnC) [100]. This target-specific AAV-gene therapy can significantly suppress tumor growth.

**Combination treatment with multiple genes and chemotherapies**

To improve antitumor efficacy, recent efforts have focused on combining AAV-mediated multi-gene therapies with chemotherapies. Several studies reported such combination treatment: AAV-based apoptin and IL24 [101], HSV-tk and endostatin [102,103], TRAIL and cisplatin [104,105], P125A-endostatin, a mutant endostatin, and paclitaxel (Fig. 3) [106], P125-endostain and carboplatin [107], type I interferon beta (IFN-beta) and trichostatin A (TSA) [108], the survivin mutant Thr34Ala and oxaliplatin [109]. In addition, several studies demonstrated that combining AAV-based gene therapy with radiation therapy [110] and focused ultrasound therapy [111] can significantly increase cytotoxicity to tumor cells.

**Clinical trials of AAV-mediated gene therapy**

Clinical applications of AAV-mediated gene therapies show great promise in the treatment of some life-threatening diseases, including hemophilia B, Leber congenital amaurosis, Parkinson’s disease, and different cancers. Hemophilia B is an X-linked disorder. A clinical trial of AAV–mediated human factor IX (FIX) gene therapy was carried out in the first group of three patients in 2000, and FIX expression was detected in the muscles and circulating systems of the three subjects [112]. Subsequently, additional AAV-based FIX gene therapy trials in humans with severe hemophilia B were performed. Manno et al. carried out a phase I and II dose escalation clinical study in patients with severe hemophilia B that reached therapeutic levels of FIX with no evidence of acute or long-lasting toxicity [113]. The Nathwani group infused a single dose of AAV-based LP1-hFIX in six patients with severe hemophilia B (FIX activity, <1% of normal values). Expression of FIX at 2–11% was detected, and 80% of the patients remained free of spontaneous hemorrhage, an

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**Fig. 4.** Detailed analysis of retinal function and structure in patients with choroideremia. (A) Pre-surgery and (B) 6 months post-surgery analysis of patient 1 showing a shift in the cloud of variable fixation (blue dots; B, white arrow) into the area of retina exposed to vector (dotted white line), but away from the area of surviving autofluorescent retinal pigment epithelium (white solid line) that was not exposed to vector. The increase in retinal sensitivity also correlated anatomically with the region of surviving retina exposed to AAV.REP1 (C, dotted line) and residual outer retina identified with optical coherence tomography scanning (D, green arrow). The thin fovea and injection site can be seen on either side of the residual retina (green arrow). The green dot (L) is the mean center of all fixation points. ETDRS = Early Treatment for Diabetic Retinopathy Study (a standard vision test). AAV = adeno-associated virus. REP1 = Rab escort protein 1. Reprinted with permission from Ref. [40]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
important manifestation of hemophilia B [50]. Meanwhile, no evidence of local or systemic toxicity of AAV-based FIX gene therapy was detected up to 40 months after gene injection [114]. Recently, AVAV carrying a codon-optimized human FIX transgene was delivered systemically to six patients with severe hemophilia B, demonstrating long-term transgene expression of FIX with improvement of the bleeding phenotype [50]. A 10-year-long AAV-mediated human FIX expression was reported in muscles, which represents the longest transgene expression so far [115].

Alpha-1 antitrypsin (AAT) deficiency, one of the most common single-gene disorders, is suitable as a target for gene therapy. A phase I clinical trial of AAV-based M-AAT gene delivery has been validated at different doses. The M-specific AAT was expressed for 1 year, with no obvious side effects [35,116]. Further, a study of AAV-mediated M-AAT gene transfer demonstrated that intramuscular delivery of rAAV1–AAT led to ongoing transgene expression for at least 1 year. A regulatory T cell (Treg) response was induced, which permitted transgene overexpression [34].

Parkinson’s disease is a severe neurodegenerative disorder, clinically characterized by degeneration of dopamine neurons in substantia nigra pars compacta. Neuritin is a functional analogue of glial cell-derived neurotrophic factor (GDNF), which protects dopamine neurons from degeneration. The delivery of AAV-based neuritin promoted long-term motor function improvement in a phase I clinical trial [117]. A double-blind, randomized, controlled trial lasting for about 2 years proved that AAV2/neuritin gene therapy for moderately advanced Parkinson’s disease is safe and feasible [118]. The loss of L-dopa is one of the main causes of progressive Parkinson’s disease, a response to declining levels of aromatic amino acid decarboxylase (AADC). A clinical phase I study of AAV2-AADC gene therapy showed safe transgene expression over 4 years [119]. These AAV-based clinical trials have validated the promising potential of gene therapies in Parkinson’s disease.

Leber congenital amaurosis (LCA) is a kind of autosomal recessive blindness retinal disease that is incurable. A mutant of retinal pigment epithelium-specific 65-kDa (RPE65) is a major cause of LCA. A phase I clinical trial of AAV2-mediated RPE65 gene therapy improved visual function, and the 3-year follow-up clinical data confirmed that AAV-mediated RPE65 gene therapy for LCA was safe and tolerable [120]. Choroideremia (CHM) is an X-linked recessive disease caused by a mutation in the CHM gene encoding Rab escort protein 1 (REP1). AAV-based REP1 gene therapy also corrected visual acuity significantly ([Fig. 4]) [40].

In addition to the conventional transgene therapies described above, several clinical trials of AAV-based immune therapy in cancer have also been performed. Di et al. carried out a clinical safety trial of cytotoxic T lymphocyte (CTL) infusion, which was induced by delivery of dendritic cells (DCs) transduced with rAAV/cancer embryonic antigen (CEA) CDNA to patients with advanced cancers. This trial reported no severe side effects in almost all of the 26 patients [121]. Another phase I clinical trial evaluating the safety and efficacy of AAV-DC-CTL-CEA treatment in patients with stage IV gastric cancer has been carried out at the Tianjin Medical University Cancer Institute and Hospital (Clinical trial.gov NCT01637805). Meanwhile, a single intra-articular infusion of AAV2 carrying a human tumor necrosis factor-immunoglobulin Fc fusion gene (AAV2-TNFR:Fc) in 15 patients showed safety and tolerability [122].

Concluding remarks

Compared to other vectors, AAV offers several advantages, including low pathogenicity, limited immunogenicity, efficient gene transfer, and long-lasting gene expression. Tremendous efforts have led to the great development of AAV-mediated gene therapy in different cancers. Although obstacles remain, promising preclinical and clinical results have opened new avenues for the efficient management of malignancy using AAV-integrated gene therapy technology.

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Conflict of interest

All authors declare that there are no conflicts of interest.

References


