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REVIEW

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Adenoviral vector-based strategies against infectious disease and cancer

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ABSTRACT

Adenoviral vectors are widely employed against infectious diseases or cancers, as they can elicit specific antibody responses and T cell responses when they are armed with foreign genes as vaccine carriers, and induce apoptosis of the cancer cells when they are genetically modified for cancer therapy. In this review, we summarize the biological characteristics of adenovirus (Ad) and the latest development of Ad vector-based strategies for the prevention and control of emerging infectious diseases or cancers. Strategies to circumvent the pre-existing neutralizing antibodies which dampen the immunogenicity of Ad-based vaccines are also discussed.

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Introduction

Ad is non-enveloped, double stranded DNA virus with icosahedral capsids. It was first discovered by Rowe and his colleagues when they tried to culture the adenoid tissue in the laboratory in 1953. Ad infection is usually mild to human beings, but sometimes could be life threatening, especially to the immunocompromised individuals. In the 1970s, the United States army developed live Ad vaccines to prevent acute respiratory disease caused by AdHu4 and AdHu7.[1] In 1991, Rosenfeld *et al* developed the first *in vivo* gene transfer using an Ad vector, and demonstrated that human α 1-antitrypsin gene delivered by the E1-E3-deleted Ad could be detected in the lung of a cotton rat.[2] In 1993, the first human gene therapy study based on Ads was performed, a 23-year-old man with cystic fibrosis homozygous received the first *in vivo* gene therapy with administration of an E1-E3-deleted rAd vector expressing the normal human CFTR, and the subsequent clinical studies were then initiated. In recent two decades, Ads have been widely applied as vaccine carriers since they are capable of eliciting T and B cell responses. Furthermore, Ads can be genetically modified to induce the apoptosis of the cancer cells, which are known as the oncolytic Ads.[3,4] Ads are not only generally safe and can replicate in almost all the living cells, but also can be expanded easily in HEK293 cells and purified by CsCl gradient ultracentrifuge, and administered through oral, intranasal or intramuscular routes without adjuvants. Here, we review the Ads' potential in vaccine development against infectious pathogens or in cancer treatment, and address the latest advances in the field.

Biological characterization of Ad

Classification of the Ad

Ads are isolated from different mammalian species, such as human being, bovine and simian, among which the human Ads and chimpanzee Ads are widely used in the laboratory research or clinical study. Human Ads include more than 50 serotypes classified into subtype A to G, and chimpanzee Ads have more than 6 serotypes.[5-7] Human Ads are distributed widespreadly in the nature and most people have been infected, thus high neutralizing antibody titers were detected among the population.[8] Human subtype C Ads are the most common Ads which usually infect the children and cause upper respiratory tract infections or urinary tract infections. Human subtype B Ads sometimes cause severe eye or urinary tract infections. Some other serotypes, such as AdHu4 from subtype E, cause acute respiratory diseases.[9] However, most of the Ad infections are mild, which promotes Ad vectors into a new era as vaccine carriers.

Genome and structure of the Ad

Ads are DNA virus with icosahedral capsids of approximately 90 nm in diameter. Several studies have illustrated the structure of the Ads by cryo-electron microscopy.[10-12] The genomic DNA of Ads is about 26–45 kb, with two inverted terminal repeats of 100–140 bp flanking at both ends. The genes that express during the life cycle of Ads are generally divided into two types: the early genes and the late genes. The early genes include E1A, E1B, E2, E3 and E4, and they are mainly responsible for facilitating the replication of Ads by changing the expression levels of related host genes. The early genes can be further classified into two types: the immediate early genes (E1A) and the delayed early genes (E1B, E2, E3 and E4). E1A promotes the expression of the delayed early genes. The E1B protein generally suppresses the apoptosis of the host cells by binding to p53, Bak and Bax proteins.[13] The late genes are mainly responsible for the lysis of the host cells, assembly and release of the virions.

Ad virions mainly comprise two types of proteins: the capsid proteins and the core proteins. The core proteins mainly include proteins V, VII, X, and they mainly function as the

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DNA-associated proteins. The V protein mainly contacts with the nucleoli of the host cells and are involved in the viral assembly process.[14,15] The VII protein plays a key role in the manipulation of DNA, such as the DNA binding, the initiation of DNA replication and the viral genome's protection, et al.[16-18] The X protein is responsible for the viral chromosome condensation.[19] The capsid proteins comprise Hexon, Penton, fiber, IIIa, VIII and IX. There're 240 trimers of hexons on the surface of the Ad virions, and the hexons are the major structural protein on the capsids.[20] On the hexons, there're several hypervariable regions which are the major neutralization sites for the Ads, and the hypervariable regions can be replaced with other foreign antigens as potential vaccine carriers.[21-23] There have 12 pentamers of pentons on the top of the 12 icosahedral vertices, and they serve as the receptors for Ad internalization into the host cells,[24] and each vertex has 12 trimers of fibers protruding from the capsid surface which are mainly responsible for the interaction with the cellular receptors to initiate the viral entry.[10,25] The IIIa proteins are on the inner capsid surface, and are mainly responsible for the correct viral assembly, stabilization of the vertex region and the assembly of the packaged genome.[11,26] The VI proteins are inside the capsids, linking the core to the icosahedral shell, and are critical lytic factors of Ads during the endosome disruption.[27] The VIII proteins provide bonds between the peripentonal hexons and are involved in the stability of the capsids.[28] The IX proteins function to dampen the innate immune response, and affect the viral tropism and stability of the capsids.[12,29,30]

Many Ads can be engineered for laboratory or clinical use. The recombinant Ads can be replication-incompetent or replication-competent. E1 gene is essential for the replication of the Ads, total or partial E1-deletion results that the vector can infect most of the living cells but cannot be expanded as it being replication-incompetent in normal cells. However, E1-deleted Ad can be propagated on dedicated helper cells, specialized cells that provide the E1 functions in trans, such as HEK 293 and PER.C6,[31] in which E1-deleted Ad is replication-competent.

Cellular receptors of the Ad

The entry of the Ads into host cells is initiated by the binding of fiber knob to the cell receptors. The CAR functions as the receptor for the fiber protein in subtype A and C-F Ads,[32-34] but in some cells, such as cancer cells and mature skeletal muscle cells, CAR is expressed in low levels.[35-37] In CAR-deficient lymphocytes, subtype C Ads can cause latent infection,[38] and the mutated CAR does not affect the tropism when Ads are administered systematically.[39] These results suggest that there might be other receptors for Ads except CAR. In fact, many other receptors for the entry of Ad have been found, for examples, CD46 or DSG2 for subtype B Ads,[40,41] and sialic acid and integrins, et al.[42-45]

After the binding of the fiber knob to receptors, the virion internalization starts through endocytosis. Generally, the endocytosis is initiated by the binding of penton bases to the integrins,[43,46,47] but some reports revealed that the uptake of Ad virions could use lipid rafts or caveolae as entry route.[48] A review article suggested that when the Ad virions were coated with charged polymers, the entry routine might be changed accordingly.[49]

Ad vector-based vaccine candidates for infectious diseases

Ad vectors are one of the most effective carriers for delivery of foreign antigens into the host cells. Compared with other viral vectors such as lentivirus, retrovirus and adeno-associated virus, etc, Ads are highly immunogenic and can induce both robust innate and adaptive immune responses in mammalian hosts. Ads have a large genome size, making the manipulation of the genetic DNA much more convenient. Unlike lentivirus or retrovirus, Ads do not integrate the viral genomic DNA into the hosts' genome, which reduces the risk of insertion mutagenesis. Adeno-associated virus is less pathogenic than Ads, but it is not yet suitable for mass production.[50] All above features make Ad a good vaccine carrier for the infectious diseases. Table 1 and Table 2 show a list of vaccine candidates based on Ad vectors[51-88] against some certain infectious diseases.

In the early stage, some Ads were modified as replicating-competent vectors with only E3 deletion which is not indispensible for the replication.[89] Nowadays, most of Ad vectors are replication-deficient with the deletion of E1 or both E1 and E3. E1-deficient vectors can only be rescued and expanded in the E1 trans-compensating cell lines. E3 deletion increases the packaging capacity of the Ad vectors, such E1-E3-deleted Ads can be incorporated with up to 7–8 kb foreign genes.[90] E4 can also be deleted, but the E4-deleted vectors only propagate in the E4-compensating cell lines.[91] The fully gutted Ad vectors were developed with containing the replication origins and packaging signals while most of the viral coding sequences were deleted. The fully gutted Ads can only be amplified with the appearance of helper virus.[90] Compared with the traditional Ad vectors, the fully gutted Ads have less toxicity caused by T cell responses, and the transgene products can be stably expressed.[92,93]

Different Ad vectors can elicit different immune responses in various laboratory animals or species.[94] A study of SIV Gag-

Table 1. List of rAd vaccine candidates in clinical trials.

Pathogens	Ad vectors	Antigens	Study models	Clinical trials	References
HIV/SIV	AdHu5, AdHu26,AdHu35	Gag,Pol, Env,Nef,GRIN	Mice, nonhuman primates, humans	Yes	51-58
Influenza virus	AdHu4, AdHu5,	HA	Mice, humans	Yes	59-62
Ebola virus	Chimpanzee Ad3, AdHu5, AdHu26, AdHu35	GP	Mice, guinea pigs, nonhuman primates, humans	Yes	72-78
Mycobactrium tuberculosis	AdHu5,AdHu35	CFP10, ESAT6, Ag85A, Ag85B, TB10.4	Mice, nonhuman primates, humans	Yes	79-82
Plasmodium falciparum	AdHu5, AdHu35, Chimapanzee Ad63	AMA1,MSP1,CSP	Mice, nonhuman primates, humans	Yes	83-88

Table 2. List of rAd vaccine candidates in pre-clinical trials.

Pathogens	Ad vectors	Antigens	Study models	Clinical trials	References
Rabies virus	AdHu5, Canine Ad type 2,AdC68	GP	Mice, fox, dog, sheep, nonhuman primates	No	63-66
Dengue virus	AdHu5	E, prM	Mice, nonhuman primates	No	67-69
MERS	AdHu5, AdHu41	S	Mice	No	70,71

specific CD8(+) T cell responses in mice vaccinated with AdHu5, AdHu26 and AdHu35, respectively demonstrated that AdHu5 was more immunogenic than AdHu26 and AdHu35, but AdHu26 and AdHu35 generated long-lived memory T cells, whereas AdHu5 elicited more terminally differentiated phenotypes of T cells.[95] In another study, AdHu35, AdHu26 and AdHu48 were found to substantially produce higher levels of IFN-γ, IL-6 and 10-kDa gamma interferon-induced protein than AdHu5 in rhesus monkeys.[96] Based on their different immunogenicity profiles, certain serotype of Ads can be selected alternatively for specific researches. Ad vectors can be administered by injection and oral immunization, both of which elicit well immune responses, while oral administration can elicit mucosa immune response compared to injection, and greatly circumvent the pre-existing anti-vector immunity.[97,98]

HIV vaccine based on Ad vector

Safe and efficient HIV vaccine is urgently needed since HIV still remains a severe public health threat. Several strategies have been developed for HIV vaccine design, of which Ad vectors are widely tested.[99] One of the most well-known clinical trials is AdHu5 based HIV vaccine which was developed by Merck, Inc.[51] In the clinical trial, the replication-incompetent AdHu5 vectors encoding gag, pol and nef genes were administered to 1494 participants at a dose of 3×10^{10} vp, while placebo administered to 1506 participants. This vaccine induced $CD8^+$ T cell responses in homosexual men, but failed to prevent the HIV infection or reduce the early viral load. Further research revealed that the vaccine appeared to increase the risk of HIV infections in the AdHu5 serotype positive individuals.[56] To explain the phenomenon, several studies have been performed and suggested that one possible mechanism was that the immune complexes of AdHu5 and anti-AdHu5 antibodies could activate the dendritic cells and $CD4^+$ T cells[100] which might serve as the targets for HIV infection.[101]

After the failure of the Merck HIV vaccine trial, other improved strategies have been tested, such as the regimen of DNA prime with AdHu5 boost. As reported by Churchyard GJ and Koup RA, et al,[53,102] a DNA plasmid encoding multiple HIV genes from multiple clades for priming at 0,1 and 2 month respectively at a dose of 4 mg, and AdHu5 expressing multiple HIV genes for boosting at 6 month induced polyfunctional $CD4^+$ and $CD8^+$ T cells as well as the anti-envelop binding antibodies, which revealed the heterologous prime-boost regimen was a potent immunization strategy for inducing both antibody and T cell responses. However, similar strategy used in another clinical trial with the regimen of priming 4 mg DNA encoding multiple HIV genes at week 0, 4 and 8, respectively, and boosting with 10^{10} pu rAdHu5 at week 24 reduced neither the rate of HIV-1 acquisition nor the viral-load set points in the participants.[103]

As the AdHu5 based vaccine carriers are not suitable for HIV prevention, other serotype Ad based vaccines, such as AdHu26, AdHu35 or chimpanzee Ad vectors have been developed.[55,104,105] In a study of AdHu26 expressing HIV-1 envelop as a new vaccine candidate, both the AdHu26-serotype positive and negative participants received a single intramuscular immunization with 5×10^{10} vp rAdHu26.[106] The result revealed that rAdHu26 elicited both systemic and mucosal envelop-specific humoral and cellular immune responses, but interestingly the individuals with pre-existing AdHu26-specific neutralizing antibodies had comparable immune responses to the AdHu26-serotype negative ones. HIV vaccines based on the rAdHu35 expressing the HIV-1 envelop antigen have been studied.[107] In this phase 1b study, 192 healthy, HIV-uninfected participants were recruited and divided into one of following groups: rAdHu35/rAdHu5, DNA/rAdHu5, and DNA/rAdHu35 in AdHu5-seronegative persons, and DNA/rAdHu35 in AdHu5-seropositive persons, and a placebo group. The participants received three doses of 4 mg DNA or just one dose of 10^{10} pu rAd at the first 2 month, then were boosted with 10^{10} pu rAd at month 6. 4 weeks post boost, the immune responses were detected. The results indicated that all regimens were generally well tolerated and similarly immunogenic, and elicit cross-clade antibody responses including envelop V1/V2-specific IgG responses.

Presently, more novel Ad vectors are being discovered and developed for the HIV vaccine design, but none of them is ready for the market, thus more improvement is needed for the Ad vector-based HIV vaccine.

Influenza vaccine based on Ad vector

Ad vectors have been applied in the development of influenza vaccine. In most of Ad-based influenza vaccines, the influenza protein, such as HA, NP or M2 is expressed by the Ad vectors to induce neutralizing antibodies and T cell responses in the host. For example, HA protein of PR8 strain (H1N1) expressed by Ads can elicit HA-specific antibodies and cellular responses against the PR8 virus.[108] Besides Ad vectored vaccine against particular strain of influenza virus, the universal influenza vaccines based on Ads have been explored. In the multivalent influenza vaccines based on the replication-incompetent AdHu5, HAs from different subtypes and NP from one subtype were expressed on the rAds. The mice were immunized intramuscularly with 10^{10} PFU of rAds twice at 4-week interval. 4 weeks post the boost, high levels of humoral and cellular immune responses were well induced and the mice were protected from lethal challenge with H5, H7 and H9 avian influenza virus subtypes.[109] In another multivalent influenza vaccine based on AdHu4 and AdHu5,[110] HA genes from the H1, H3, H5 subtypes of influenza virus were expressed by the Ad vectors, and then immunized mice by rAdHu4-prime/rAdHu5-boost regimen at a doses of ranging from 10^7 to 10^{10} vp with a 4 week interval. The

vaccination results revealed that the highest dose vaccine groups were 100% protected from the heterologous lethal challenge of different subtypes of influenza virus, indicating that Ad-based multivalent influenza vaccines had great potential in the prevention and control of the influenza virus.

Ad-based influenza vaccines have been tested in clinical trials. A non-replicating AdHu5 vector expressing HA from avian influenza and a TLR3 ligand were tested in humans.[60] Most of the participants received only one dose of Ads by capsule, with titers ranging from 10^8 to 10^{10} IU, but some were boosted with another dose of 10^9 IU Ad at 4 weeks post prime. The vaccination results revealed that the antigen specific cytotoxic and IFN-γ responses were induced in a dose dependent manner and cytotoxic responses increased after boost, which demonstrated that Ad-based vaccine administered orally could induce antigen specific immune responses and was safe as a vaccine candidate.[60] AdHu4 based avian influenza vaccine was developed and tested in a clinical trial. AdHu4 expressing HA of H5N1 was orally administered 3 times at a dose of 10^7 to 10^{10} vp within 56 days, and then boosted with 90 μg inactivated H5N1 viruses. The results demonstrated that cellular immune responses were well induced and oral administration of Ad might enhance the efficacy of poorly immunogenic vaccines such as H5N1, but the limitation of this study was that the HI titers were hardly measured.[61] By orally administered replication-competent AdHu4 vaccine, another improved strategy was reported.[111] In the study, the individuals were primed with AdHu4-H5-Vtn three times at dose of 10^7 to 10^{10} vp in 56 days, and then boosted with the 90 μg unadjuvanted licensed inactivated H5N1 subunit vaccine at 3.5 to 12 months. The new regimen induced high HI titers compared with unprimed individuals, which compensated for the disadvantages in the previous vaccination routine.

With the development of RNAi technology, Ad based RNAi strategies have been applied in prevention and control of influenza infection. For example, a novel chimpanzee Ad termed as AdC68 was used as the microRNAs expression vector and tested in mice. AdC68-expressing amiRNAs targeting M1, M2 or NP genes of influenza virus could efficiently suppress the viral replication and confer complete protection from the lethal challenge of H9N2 and H5N1.[112]

Ebola vaccine based on Ad vector

Ebola virus was firstly discovered in 1976 with the outbreaks in Democratic Republic of Congo and Sudan,[113,114] but the outbreak in Africa in 2013 made it a public concern again.[115] There have been several strategies for the Ebola vaccine development, of which the Ad vectors are selected as a priority.

The NIH vaccine research center firstly developed a vaccine based on heterologous prime-boost regimen in 2000. In the research, the primates were firstly immunized with a DNA vaccine three times at 0, 4, 8 weeks at a dose of 4 mg, and then boosted with 10^{10} PFU AdHu5 which expressed GP protein of Ebola virus 20 weeks post prime. The results showed high antibody titers and $CD4^+$T cell responses were induced in vaccinated animals, and the vaccinated groups had a higher survival rates than the control groups after challenged with Ebola virus.[116] Since this experiment took more than six months to complete the immunization flow chart, researchers developed an accelerated immunization method for the vaccination.[117] In the accelerated experiments, the animals were given AdHu5 expressing GP and NP of Ebola virus twice at doses of 2×10^{12} vp with a 9-week interval. The vaccinated animals were challenged with lethal Ebola virus and the protection was highly effective since the Ebola-specific CD8+ T cell and antibody responses were well induced. In the subsequent study, the animals were only primed with rAd–GP/NP and challenged 28 days later, but they still had high survival rates with either low or high doses of challenged virus. As the AdHu5-based Ebola vaccine showed a good prospect in the non-human primates, the first clinical trial based on AdHu5 was performed,[72] with a recombinant vaccine encoding the envelope GP from the Zaire and Sudan Ebola virus tested in a randomized, placebo-controlled, double-blinded, phase I human study. Thirty-one healthy adults received a single dose of the rAdHu5 at 2×10^9 vp (n = 12), or 2×10^{10} vp (n = 11) or placebo (n = 8). The results indicated the antibody responses to the two GPs in subjects were not well balanced. In the low dose group, antibody responses to Zaire GP were 50%, and 58% to Sudan GP. However, the antibody responses in the high dose group were 55% and 100%, respectively. In this study, the pre-existing neutralizing antibodies to AdHu5 was also noted, but it didn't appear to affect the T cell response to Ebola GP since 32% to 82% subjects responded with more $CD4^+$ than $CD8^+$ T cells.

Recently, Ebola vaccines based on the other serotypes are being developed, one of which is the chimpanzee Ad serotype 3 (cAd3). In a clinical trial of cAd3 based Ebola vaccine, 20 volunteers were recruited and divided into 2 groups. The volunteers in each group received the rAds expressing the GP protein from both Zaire and Sudan Ebola virus. One group received high titers of Ads with 10^{11} vp while another received 10^{10} vp, and two individuals in the high dose group experienced transient fever. The final results demonstrated that the rAds induced well specific antibody responses and T-cell responses, with higher levels of responses in the high dose group.[118] In another trial based on cAd3, 60 volunteers who were divided into 3 groups received a single dose of Ads ranging from 1×10^{10} vp to 5×10^{10} vp, and only 2 volunteers developed transient fever. After vaccination, specific antibody responses and T-cell responses were successfully elicited, but the levels were lower than those detected in the non-human primates.[119] In a recent phase I clinical trial which was performed between Oct 8, 2014, and Feb 16, 2015, 91 participants in Mali and 20 in the USA were recruited to receive cAd3 expressing GP of Ebola with a single dose ranging from 10^{10} to 10^{11} pu. After the prime of Ads, some Malians were boosted with vaccinia Ankara expressing GP of Zaire Ebola virus and filovirus antigens (MVA-BN-Phyllo). The vaccination results showed that 1×10^{11} pu single-dose rAds could suffice for a efficacy trials and the regimen of MVA-BN-Phyllo boosting could confer long-lived protection which might be needed for the healthcare workers.[77]

Other vaccines against infectious diseases based on Ad vector

Ad vectored vaccines have been developed for some other infectious diseases besides influenza virus, HIV and Ebola virus. A tetravalent dengue virus vaccine based on the rAds was tested in non-

human primates. In the study, the prM and E gene from different subtypes of dengue virus were expressed by Ads. The vaccination included two doses of 10^9 IU rAds administration with a 57-day interval, and 85 days or 253 days post prime, the animals were challenged with dengue virus. The vaccination results revealed that the animals produced high-titer antibodies that could neutralize all four serotypes of dengue viruses *in vitro*. The challenge studies showed that significant protection from viremia was observed against all four dengue virus serotypes, but the protection efficacy was better in dengue-1 and dengue-3 challenges than in dengue-2 and dengue-4 challenges.[67]

In addition to the Ad-based virus vaccine, Ads have been developed for the bacteria vaccine or protozoan vaccine. Mycobacterium tuberculosis causes serious bacterial infections in humans, and a vaccine based on AdHu5 expressing Ag85A has been tested in a phase 1 clinical trial. The results showed the polyfunctional CD4+ and CD8+ T cell responses were well stimulated, and the pre-existing neutralizing antibodies to AdHu5 had little influence on the potency of the vaccine.[82] Malaria, which is caused by Plasmodium falciparum, poses a serious threat to public health. An AdHu5 vector encoding the apical membrane antigen 1 and circumsporozoite protein of P. falciparum was evaluated in a clinical trial.[85] In the study, the DNA prime with Ad boost regimen was proved to be effective in eliciting specific T cell responses. Furthermore, some other serotypes of Ad, such as AdHu35 were developed for the malaria vaccines which listed in Table 1.

Human Ad serotypes such as AdHu5 have been extensively used for vaccine development mainly due to their excellent immunogenicity and safety. As the effect of pre-existing immunity on AdHu5-based vaccines, the clinical use of AdHu5 is greatly limited, while the rare human serotypes of Ads or non-human-originated Ads such as chimpanzee Ads have been extensively tested in both preclinical research and clinical trials.

Ad vector-based cancer therapy

Oncolytic Ads have shown great promise in cancer treatment since they exhibit distinct anti-cancer characteristics. During the life cycle of Ads, the Ad-infected cancer cells can be lysed in the end, and after the release of the Ad virions, they infect other cancer cells to initiate the next life cycle. Generally, two strategies are widely adopted for the modification of oncolytic Ads. The first one includes Ads expressing the therapeutic genes or combining RNAi technology to degrade the tumor promotion proteins. The second one mainly focuses on the capsids modification of the Ads, making Ads have specific tropism for the tumor cells or replicate to higher titers in the tumor tissues than in normal ones. These two strategies might be integrated to generate better anti-cancer effect.

One of the most well-known Ad-based anti-cancer drugs is the Advexin.[120] It is an E1-E3-deleted AdHu5 vector expressing p53 under the drive of CMV promoter in the E1 region. The Advexin has been applied in multiple cancer treatments, such as head and neck cancer, breast cancer and colon cancer, et al.[121-123] In the hand and neck squamous cell carcinoma, the Advexin was tested in a phase III clinical trial, patients were randomly treated with either Ad-p53 intratumorally on days 1 and 3 of each week at a daily dose of 2×10^{12} vp or methotrexate once weekly at a starting dose of 40 mg/m^2, and each treatment cycle include 21 days. The results revealed that the vector was well tolerated and the anti-tumor activities were significant.[124] Another well-known drug against glioma is Sitimagene Ceradenovec. The drug is an E1-E3-deleted, AdHu5-based vaccine that expresses the herpes simplex virus' thymidine kinase at downstream of CMV promoter in E1 cassette. In the phase III trial, 250 patients were recruited with 124 in the AdHu5-treated group while 126 in the standard care group. Different groups received standard care plus injection of 1×10^{12} vp rAd or just standard care alone. Almost all the individuals experienced adverse events in the trial. The clinical results suggested that use of Sitimagene Ceradenovec increased the survival time or re-intervention in patients with newly diagnosed supratentorial glioblastoma multiforme.[125]

Transduction of specific tumor antigen into dendritic cells is one of the most effective strategies against cancer. In an in vitro study, the DCs transduced with rAds expressing livin α induced strong specific cytotoxic T lymphocytes against different cancer cells.[126] Ads can be armed with immune modulator such as GMCSF or REIC to induced cytotoxic T lymphocytes against cancers. In a clinical trial, the patients received the combination treatment of Ad-GMCSF and alkylating agents had higher survival rates than the ones only treated with alkylating agents, possibly due to the activation of anti-tumor T cells.[127] In a E. G7 tumor-xenograft mouse model, Ad-REIC induced tumor-associated antigen specific cytotoxic T-lymphocytes, and the secreted REIC protein in the tumor generated a proper micro-environment for inducing of activated dendritic cells, resulting in decreased tumor size in the tumor-bearing mice receiving the Ad-REIC compared to the control groups.[128]

RNAi technology is widely used in the downregulation of the specific gene's expression by sequence-specific degradation of the RISC complex.[129] The application of RNAi technology based on Ads may be extremely effective since the small RNA molecules can be steadily expressed, thus the targeted protein remains at low levels for long. One of the firstly used RNAi technologies based on Ads was the vascular endothelial growth factor (VEGF)-specific targeting small RNAs. To induce and maintain the long-lasting silencing of VEGF, the study constructed E1A-mutated, E1B-deleted Ads with shVEGF expressing at the E3 region under the drive of U6 promoter. After the vaccination of the Ad-shVEGF in tumor-bearing mice, potent anti-angiogenesis was induced and resulted in tumor suppression and survival benefits.[130] Recently, a study revealed that the amiRNAs based on the AdC68 vector could downregulate the survivin which was highly expressed in tumors, and the rAdC68 caused blockade of mitosis and cell cycle arrest at the G2/M phase. In the tumor-xenograft nude mice models, survivin-targeting amiRNAs expressed by rAdC68 effectively delayed growth of hepatocellular and cervical carcinomas.[131]

Ads have great potential as anti-cancer vectors. However, the clinical use of Ads is limited due to their limited infectivity in some cancer cells. Modifying the tropism of the Ads is an alternative way to generate better anti-cancer effect. In a recent study, the epidermal growth factor-like domain of the human heregulin-α (HRG) was inserted into the HI loop of AdHu5 fiber without adverse effect on the Ad growth or yields. The fiber-modified Ad virions showed enhanced infection of cells expressing the cognate receptors HER3/ErbB3 and HER4/

ErbB4, so the HER3-expressing Chinese hamster ovary (CHO) cells could be transduced by the HRG-modified virus, but not by wild type virus.[132] Other studies showed that the fiber-modified Ads had specific tropism to different cancer cells, which may provide a new strategy for Ad based cancer therapy.[133,134]

Capsid-incorporation of foreign antigen into ad virions as vaccine candidate

The most common method for Ad vaccine development is the expression of the foreign antigens in the E1 or E3 region of Ad vector as previously described in Table 1 and Table 2. However, pre-existing antibodies to the vectors may result in the failure of the vaccine. The "antigen capsid-incorporation" strategy has been developed to compensate for the drawbacks associated with the conventional antigen-expression system by the Ad vector to evade the pre-exisiting immunity. The Ad capsid proteins such as hexon, penton base, fiber, and pIX have variable sites for the antigen incorporation.[135,136]

Hexon is the most abundant structural protein on the capsid and has several hypervariable regions which can be modified to display the foreign antigens without affecting the Ad's rescue and infectivity. For example, the AdC68 vectors were modified to express a linear B-cell epitope of the ectodomain of matrix 2 (M2e) of influenza virus within hypervariable regions 1 (HVR1) or HVR4 of the Ad hexon. Additional vectors with wild-type or M2e-modified hexon with influenza A virus NP as a transgene product in the E1-deleted region were also tested in the study. The vaccination regimen included priming with 10^{10} vp rAd and some mice boosted 2 months later. The pre-clinical study demonstrated that Ads expressing M2e within HVR1 of hexon induced higher magnitude and avidity of M2e-specific antibody responses than those carrying M2e within HVR4 or vectors expressing the M2e as part of a transgene product, and the M2e-specific antibody responses could be boosted by a second dose of the HVR1 hexon-modified vector but not by repeated immunization with the HVR4 hexon-modified vector.[23] Besides influenza virus vaccine, other studies reported that the insertion of the neutralizing epitopes of HFMD virus into hexon could elicit neutralizing antibodies against HFMD virus lethal challenge in the mice models.[22,137] As the HVRs of hexon contain the neutralizing epitopes of Ads,[20] the hexon-modified Ads might change the immunogenicity compared to the wild type Ads, and the anti-sera from the hexon-modified-Ad vaccinated animals cannot well neutralize the wild type Ads, which provides a good platform for the prime-boost regimens for Ad based vaccines.[22]

Besides hexon, fiber can be engineered as an antigen-display system. Fiber modification makes Ads have specific tropism for cancer cells as above described, and can be incorporated with foreign antigens as vaccines against infectious diseases as well. A vector of AdHu5 expressing the 14-mer Pseudomonas aeruginosa immune-dominant outer membrane protein F (OprF) epitope 8 (Epi8) in five distinct sites of fiber was immunized in the mice. The results demonstrated that the FG-loop and HI-loop inserted sites were better than the other insertion sites in fiber since higher levels of protective immunity against *P. aeruginosa* were induced by FG-loop or HI-loop modified vectors.[138] The penton base and pIX were tested for antigen-incorporation in some studies.[139-142] However, compared with the other three proteins on the capsids, the penton base was rarely incorporated with foreign antigens perhaps due to the structural constraints.

Outlook and conclusions

Generally, Ad vectors are easy to be manipulated for genetic modification and capable of inducing potent antigen-specific immune responses. Most of the Ad species are rarely pathogenic to humans. Compared to the conventional vaccines, Ad vector-based vaccines can express a wide range of antigens from virus, bacteria or protozoan, and elicit long-term immune responses against infectious diseases. Despite the pre-existing neutralizing antibodies to the human Ads, the rare serotypes of Ads from different species have been developed to circumvent the disadvantages. All above advantages make Ads very attractive and potential vaccine candidates. Furthermore, Ad vectors show priority in anti-cancer research since they can be armed with therapeutic genes or modified to expand to higher titer in tumors than in the normal tissues. Many Ad vectors have been studied in animals against either infectious diseases or cancers, and revealed a good prospect of the further development.

Despite the incomplete success of Ad-based vaccines, Ad vectors still show great potential and are being extensively tested in the clinical trials recently. With more information obtained from Ad-related clinical trials, our understanding of the Ad vectors will be greatly enlarged, which will further promote the use of Ad vectors in the prevention and control of infectious diseases and cancer.

Abbreviations

Ad	adenovirus
CAR	coxsackie and adenovirus receptor
AdHu,	human adenovirus
rAd	recombinant Ad
DSG2	desmoglein 2
HIV	human immunodeficiency virus;
SIV	simian immunodeficiency virus
MERS	Middle East respiratory syndrome coronavirus
HA	hemagglutinin
NP	nucleoprotein
HI	hemagglutination-inhibiting
GP,	glycoprotein
amiRNA	artificial microRNA

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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