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Application of gene therapy with viral vectors in infectious and noninfectious diseases

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Authors
Sepideh Saeb[1,]
Mehrdad Ravanshad[2]*

1.Qaen School of Nursing and Midwifery, Birjand University of Medical Sciences, Birjand, Iran.
2.Department of Virology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

***Corresponding authors:**
Department of Virology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran. E-mail:
,
Ravanshad@modares.ac.ir

ABSTRACT

Virus-based vectors, also called viral vectors are being studied in the field of gene therapy because of their innate biological and structural properties. Their ability to protect and specific delivery of genetic elements into the cells, promising results in the pre-clinical studies, going through clinical trials and approval of some products as a therapeutic option in some cancers introduce viral vectors as a powerful tool in the field of gene therapy. In this review, first an introduction about viral vectors is presented and then some studies about application of viral vectors in various fields of human diseases such as prevention and treatment are briefly discussed.

Key words: viral vector, gene therapy, infectious diseases, noninfectious diseases

1. An introduction to Viral Vectors

The idea of use of genes in human diseases, especially in the field of treatment, was introduced in the 1970s (1).

Gene transfer to target tissues and cells using conventional transfection methods has some problems such as non-specific vector diffusion. Viruses, with their unique structural and biological properties, can protect genetic information well and transfer it into the cells (2).

The ability to enter the host cell specifically, replicate in the cells, and controlled expression of gene are some of the benefits that have made viruses powerful tools for transfer of therapeutic genes. But the important point is that many viruses that are used as vectors are potentially pathogenic. Therefore, they must be modified in such a way that only the elements of the virus that are essential for transfer to the target cell and transgene expression remain and other

components involved in pathogenicity are removed (3).

Adeno-Associated Virus (AAVs), adenoviruses, retroviruses, lentiviruses, and herpesviruses are among the most important viral vectors, each of them with their own advantages, disadvantages, and characteristics. Lundstrom provides examples of viral vectors used in gene therapy, the genomic class of each virus, its packaging capacity, and its important characteristics (4). They are mentioned in Table 1.

Table1. Examples of viral vectors used in gene therapy (4).

Virus	Genome	Insert Capacity	Features
Adenoviruses Ad5	dsDNA	<7.5 kb	broad host range transient expression strong immunogenicity
AAV AAV2, 3, 5, 6, 8, 9	ssDNA	<4 kb	relatively broad host range slow expression onset chromosomal integration immune response
Herpes simplex HSV1, HSV	dsDNA	>30 kb	broad host range latent infection, long-term expression low toxicity, large insert capacity
Retroviruses MMSV MSCV	ssRNA	8 kb	transduces only dividing cells long-term expression random integration
Lentiviruses HIV-1, HIV-2	ssRNA	8 kb	broad host range low cytotoxicity, integration long-term expression
Alphaviruses SFV, SIN, VEE, M1	ssRNA	8 kb	broad host range extreme transient expression low immunogenicity neuron- and glial-specific mutants
Flaviviruses Kunjin, West Nile, Dengue virus	ssRNA	6 kb	relatively broad host range transient expression packaging system
Rhabdoviruses Rabies, VSV	ssRNA	6 kb	relatively broad host range high transient expression low immunogenicity
Measles virus MV-Edm	ssRNA	6 kb	transient expression oncolytic strains
Newcastle disease Virus	ssRNA	6 kb	replication in tumor cells improved oncolytic vectors
Poxviruses VV	dsDNA	>30 kb	broad host range, large inserts replication-competent vectors
Picornaviruses Coxsackievirus	ssRNA	6 kb	oncolytic strains

AAV, adeno-associated virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MMSV, M murine sarcoma virus; MSCV, murine stem cell virus; SFV, Semliki Forest virus; SIN, Sindbis virus; VEE, Ven equine encephalitis virus; VSV, vesicular stomatitis virus; VV, vaccinia virus.

2. Viral vectors and infectious diseases

Viral vectors are also widely used in the prevention and treatment of acute and chronic infectious diseases. Here, it is noted to the recent pandemic of coronavirus and Human Immunodeficiency Virus (HIV) infection, as the examples.

2-1. Viral vectors and SARS-CoV-2 infection:

A recent pandemic caused by the SARS-CoV-2, known as COVID-19 disease, has infected millions of people worldwide. The need to prevent this disease, stop transmission and reduce severe cases and mortality, has led many research teams around the world to design appropriate vaccines that these vaccines are in different phases of pre-clinical and clinical trials and some of them are now using in populations.

In general, there are several platforms for designing vaccines against infectious agents, especially viruses:

1.Classic vaccine platforms: which can be divided into two groups based on virus and protein. Virus-based vaccines include inactivated virus and attenuated virus. Protein-based vaccines include protein purified from virus or virus-infected cells, recombinant proteins, or virus-like particles (5).

2. Next Generation Vaccine Platforms: The main advantage of this generation of vaccines is that they can be developed only based on the sequence information. In other words, knowing the important proteins of the virus in stimulating immunity against infection or disease and having a gene sequence of a protein is enough to start the vaccine production process and there is no need to cultivate the virus. These vaccines include DNA-based vaccines, RNA-based vaccines, antigen-presenting cells, and viral vectors (5).

As mentioned earlier, in viral vectors, certain genes of the virus that are responsible for its pathogenicity are deleted, and the genes encoding the vaccine virus antigens are cloned into the viral vector using recombinant DNA techniques (5).

Viral vector vaccines can be replicating or non-replicating. In replicating vectors: after infecting a cell and expressing viral antigen, they can produce new viral vectors that infect new cells and express the viral antigen of the vaccine. In non-replicating forms, the vector enters the cell and the vaccine antigen is expressed, but no new viral particle is produced (5).

Because viral vector vaccines express antigens endogenously, they can stimulate both cellular and humoral immune responses (5).

By the time of writing of this text, the World Health Organization estimates that there are 196 vaccines in the preclinical phases and 153 vaccines in the clinical phases, about 19 % of them are based on viral vectors or a combination of viral vectors and other next generation vaccine platforms such as antigen-presenting cell (6).

The most important of these viral vector vaccines are the Oxford – AstraZeneca, Sputnik V, and Ad5-nCoV vaccines, all of them are based on the adenovirus vector, which expresses the corona virus spike protein. The Oxford – AstraZeneca vaccine uses chimpanzee adenovirus, the Sputnik V vaccine: adenovirus types 5 and 26, and the Ad5-nCoV vaccine uses adenovirus type 5 (7-9).

2-2. Viral vectors and HIV-1 infection: Various studies have also been performed on viral vectors in different aspects of HIV-1 infection which is a chronic infectious disease. Here are some examples of these studies specially in the field of potential prevention and cure strategies:

In one study, targeting the CCR5 (HIV-1 co-receptor) and the R region of the virus LTR by a lentivector containing shRNA in a mouse model effectively inhibited HIV infection (10). This finding was confirmed in other experiments performed on cell culture (11). Promising results of preclinical studies led to the entry of RNA interfrance into phase one of the clinical trial (12). In another study in non-human primates, the Vesicular Stomatitis Virus (VSV) vector, which expresses the Gag and Env proteins of HIV-1, stimulated strong cellular and humoral immune responses. Vaccination of the animals with this viral vector protected them against challenge with the recombinant and pathogenic form of HIV / SIV (13).

In the field of vector immunoprophylaxis of HIV-1 infection, a study used an AAV vector containing broad neutralizing antibodies (bNAb) against the V2 region of the virus envelope protein. A single dose of AAV injection induced effective expression of antibodies in cell culture and immunocompetent mice (14). This long-term and systemic expression of neutralizing antibodies has the advantage over passive antibody transfer (15).

Also, in order to inhibit HIV-1 infection, viral vectors containing the intrinsic immunity components against HIV-1 have been tested in vitro. For example, Krista et al. designed a lentivector which the mutant form of the cellular antiviral factor APOBEC3G (A3G) was cloned in it. This mutant form, called A3G-D128K, is resistant to inactivation by the virus Vif protein. This lentivector was able to effectively deliver A3G-D128K to the target cell and potentially inhibit the spread of infection in T cell lines (16). After infection of the certain cells of the immune system with HIV-1, the virus can integrate its genome into the genome of these cells and establish a latent infection. These latent viruses are not recognized by the immune system and the Antiretroviral Therapy (ART) regimen is not effective against them. Nowadays several strategies to eradicate and manage these latent reservoirs have been developed.

For example, in an in vitro study, we tried to reduce the virus latency reservoir in the brain. For this purpose, the histone deacetylase inhibitor "Romidepsin" was utilized as the HIV-1 reactivator from latency in microglial cell line. Also, in order to remove the reactivated cells, the AAV viral vector containing thymidine kinase gene which is controlled by the HIV-1 LTR structure, was used. So, after virus reactivation by romidepsin, virus trans activator protein, "Tat", is produced. Tat has a stimulating effect on the LTR and induces TK expression. Because TK expression is controlled by HIV-1 LTR structure, cell apoptosis will be limited to the cells that are reactivated and express TK gene.

The results showed a high and considerable percentage of the cellular reactivation and apoptosis in comparison to the control groups. So, it indicates the effective function of the AAV viral vector to remove the reactivated cells. Findings of this study that are based on a method to targeted depletion of the reactivated cells by viral vector, can be useful for latency and cure researches in the future (17).

3. Viral vectors and non-infectious diseases

The application of gene therapy, both in the form of viral vectors and non-viral vectors in non-infectious diseases such as CNS disorders, different malignancies and genetic disorders such as hemophilia is very popular today and there are many studies in this field (18, 19).

3-1. Malignancies: In a variety of malignancies, viral vectors can act as immunomodulators or have tumor suppressive effects, depending on the type of virus and the genetic modification applied. Glioma, glioblastoma, colorectal, kidney, pancreas and prostate cancer, melanoma and

some blood malignancies are among the cases that have been studied with a variety of viral vectors containing tumor suppressor and antitumor genes in clinical trials (4).

As a result of these efforts, three drugs IMLYGIC (based on HSV-1 vector containing GM-CSF gene, melanoma recurrence), YESCARTA (based on retrovirus vector containing anti-CD19 CAR gene, some types of B cell lymphoma) and KYMRIAH (based on lentivirus vector, which contains the anti-CD19 CAR gene, some types of B cell lymphoma and leukemia) are the drugs that have received FDA approval (20).

3-2. Central nervous system (CNS) disorders: Treatment of CNS disorders has always been challenging for reasons such as the presence of the blood-brain barrier and the side effects of common drugs on nervous functions, and gene therapy can allow long-term improvement of the disorders with a single treatment approach. Different vectors can be used, including viral vectors, especially lentiviruses and AAVs (21).

AAV viral vectors due to lack of specific pathogenicity in humans, weak or lack of previous immune response to them, a wide range of serotypes known to infect different types of cells, access to various tissues in the CNS and long-term gene expression, have been studied and researched more than others and have had promising results (3, 22).

The use of AAV vectors in a wide range of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, developmental disorders, neurotransmitter disorders, lysosomal storage diseases and etc. shows the importance and potential of these viral vectors in treating or slowing the progression of these disorders. The mechanism of gene therapy for these viral vectors can include gene silencing, immunotherapy, or gene replacement (23-27).

For example, in a study conducted in Iran, it was found that the AAV viral vector containing IL-4 gene, an anti-inflammatory cytokine that plays an important role in altering microglial cell activity and inflammatory responses in Alzheimer's disease, could Inhibits the production of the most important proinflammatory cytokine induced by the amyloid β protein. Accumulation of amyloid plaques is seen in Alzheimer's (28).

3-3. Genetic disorders: Hemophilia A and B are X-linked congenital blood disorders that are caused by mutations in genes encoding coagulation factors VIII (FVIII) and factor IX (FIX), respectively (29).

Successful treatment of hemophilia with AAV vector containing FVIII and FIX genes is one of the best examples of use of viral vectors in gene therapy (30, 31). In another study, genetic modification in cord blood-derived mesenchymal stromal cells using lentivirus containing the FIX gene led to long-term production of this blood factor (32).

Lundstrom summarizes some of the clinical trials performed using viral vectors containing the relevant genes in various diseases and summarizes their results (4). They are mentioned in Table 2.

Gene therapy can be done in two ways, in vivo and Ex vivo. According to figure 1 that it is designed by Bulcha et al., in vivo gene therapy means the direct administration of a gene to a patient. In vivo, the patient's cells or allogeneic source cells are extracted, genetically modified by vector therapy, and re-injected into the patient's body after being selected and propagated in cell culture (33).

Table 2. Examples of clinical trials performed using viral vectors (4).

Disease	Viral Vector	Response
Hemophilia A	AAV-FVIII/FIX	Cure of hemophilia
Hemophilia B	Lenti-FVIII	Potential cure
	Lenti-FIX	Life-long production of FVIII
Cancer	Enadenotucirev	Good safety, no serious adverse events in phase I
	HSV HF10	Good safety, antitumor activity
	HSV HF10	Combination therapy anti-CTLA-4
HGG	Toca 511	Improved survival
	Toca 511/FC	Phase II/III trial in progress
Glioblastoma	HSV G207	Antitumor activity in Phase I
	HSV G207	Design of phase I trial for children with glioblastoma
CGD	Gamma RV	Resolution of infections, but malignant transformation
ATC	MV-NIS	Targeting iodine-resistant ATC
Colorectal CA	Oncolytic VV	Induction of immune response
	NDV	Prolonged survival of patients in phase II study
Kidney CA	LipoSFV-IL12	Transient IL-12, repeated injections
Pancreatic CA	PANVAC-VF	Failure in phase III, encouraging results in new phase I trial
Prostate CA	NDV-TAA	Improved survival in phase II
	VEE-PSMA	Neutralizing antibodies in phase I
Melanoma	NDV	Phase II/III failed to show superiority to control
	CVA21	Anti-tumor activity in melanoma patients
	CVA21 + PLMab	Overall response rate 60%, stable disease in 27% of patients
	LipoSFV-IL12	Transient IL-12, repeated injections
Solid tumors	NDV PV701	Progression-free survival
CF	Lenti-hCEF-CT	Expression, toxicity and integration profiles support for clinical trials

AAV, adeno-associated virus; ATC, anaplastic thyroid cancer; CF, cystic fibrosis; CGD, chronic granulomatous disease; CVA21, Coxsackievirus CVA21 strain; FIX, Factor IX; FVIII, Factor VIII; Gamma RV, gammaretrovirus; HGG, high-grade glioma; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LipoSFV-IL12, liposome-encapsulated Semliki Forest virus-interleukin-12; MV-NIS, measles virus-sodium iodide symporter; NDV-TAA, Newcastle disease virus-tumor associated antigen; PANVAC-VF, vaccinia-fowlpox virus; PLMab, pembrolizumab; shRNA, short hairpin RNA; VEE, Venezuelan equine encephalitis virus; VV, vaccinia virus.

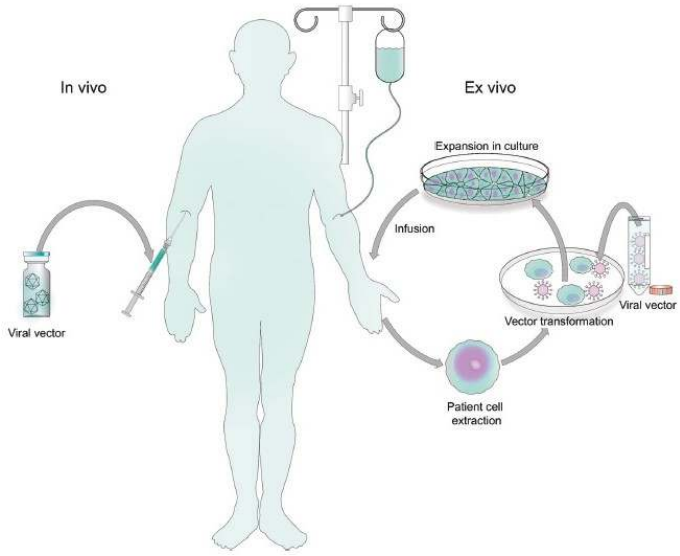

Figure1. In Vivo and Ex vivo gene therapy (33).

4. Providing systems such as CRISPR through viral vectors

With the introduction of CRISPR-Cas9 genomic editing technique, potentially powerful tools in the treatment of some diseases such as cancer were presented to researchers (34). Along with other non-viral transmission tools, AAV, lentil, and adenovirus vectors have been used to deliver CRISPR-Cas9 components (35). AAV vectors have made the most advances in in vivo researches (36).

In a study for hemophilia: Cells expressing the mutant FIX gene in canine were generated and attempted to repair the mutation by HDR using a (Tet-on) -inducible CRISPR / Cas9 system and a modified donor. (Tet-on) -inducible CRISPR /

Cas9 system was cloned in adenovirus type 5 vector and donor in AAV serotype 2 vector. The results of this study showed that HDR in combination with viral vector delivery system has promising results in correcting the FIX mutant gene in the cell model (37).

5. Discussion

There are several viral and non-viral methods for delivering genes to the target tissue, such as hydrodynamic transfer, electroporation, lipid nanoparticles, etc. each of them has its own application. Over the past 5 years, the field of gene therapy has faced a wave of drugs based on viral vectors and they have made it possible to use different drug platforms. Currently, a large number of studies are based on the three viral vectors: adeno, AAV and lentivectors (38).

However, despite promising successes and results, there are still challenges in this area that have sometimes limited the use of viral vectors (33). Previous immune responses against some adenovirus types, the small size of the AAVs genome, and the possibility of lentiviruses integrating into the host genome are some considerations when designing a gene therapy strategy with viral vectors (39).

Gene therapy has a 40-year history. Considering the number of studies, especially clinical trials, the perspective of viral vectors in the field of treatment, prevention, etc. seems bright, and more detailed studies on the biology of viruses and new techniques in the field of gene therapy can be invent appropriate methods with the least side effects and the most efficiency.

Conflicts of interest: The authors declare no conflicts of interest.

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