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Review

Viral/Non-Viral Vectors in DNA/RNA Delivery Technology

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Abstract

Viral and non-viral vectors for nucleic acids (DNA/RNA) therapeutics are important in development of pharmaceutical industries. Although viral vectors have shown significant impact in transfection of DNA/RNA, but numerus studies have shown that non-viral vectors are also effective for the safe and targeted delivery of DNA/RNA to exact location in the body with high percentage of efficacy, safety, and low-immunogenicity. It is also important to protect the nucleic acids from degradation and large-scale production capability at low cost. This review article discusses the potential applications of viral vectors in DNA/RNA delivery technology, while some of the applications of non-viral vectors are compared with viral vectors.

Keywords

Viral; non-viral; DNA/RNA therapeutics; nanoparticles; biodegradable polymers

1. Introduction

DNA and RNA-based therapeutics is an emerging technology for the delivery of genetic materials to the cells for stable transfection. There are mainly two approaches for the delivery of DNA/RNA into the cells and are divided into viral and non-viral vectors. Although among them, viral vectors are very powerful and common for the delivery of genetic materials such as DAN and RNA enable individualized approaches to the treatment of diseases including cancer, diabetes, AIDS, and tuberculosis. Development of viral vectors in delivery of DNA/RNA is due to their high performance in transfecting many *in vitro* cell lines as well as *in vivo* applications. Therefore, there are many attempts in using different viral vectors as carrier of genetic materials. It is also well known that different viruses in nature transfect their host body in a similar way with high level of efficacy. This makes viral vectors as the potential available candidates for DNA and RNA delivery.

This review article focuses and emphasizes on the potential applications of viral vectors in DNA/RNA delivery systems in comparison with non-viral vectors.

2. Viral Vectors Technology

2.1 Vaccinia Virus

Vaccinia virus is a member of the Poxviridae family that contains a linear double-stranded DNA genome of about 190 kbp in length with a high number of genes (~250) [1]. It has been vastly used as a smallpox vaccine and an oncolytic agent with comparable safety [2-4]. In addition, poxvirus vectors have also been employed in the fabrication of vaccination, cancer immunotherapy, and oncolytic cancer therapy due to the intensive expression, but short-lasting of the transgene and cytolytic properties [5, 6]. The complex life cycle of vaccinia involves two mechanisms of infection via separate forms of infectious particles, namely intracellular mature virions and extracellular enveloped virions. The former are the main product of viral lysis, while the latter are actively shed by infected cells [7]. In comparison to other agents, vaccinia allows high levels of viral gene expression, the capacity to spread cell-to-cell, rapid replication, and lysis of infected cells. Its activity is not prevented by therapeutic irradiation [8] and hypoxia [9]. Various strains of vaccinia virus are currently being investigated in preclinical and clinical trials, including Lister, Western Reserve, the Wyeth, and Copenhagen strains [10-13]. Pexa-Vec (pexastimogene devacirepvec; JX-594) is derived from a Wyeth strain and is regarded as the most advanced vaccinia virus oncolytic product. It is an armed and targeted oncolytic and immunotherapeutic vaccinia virus, causing the disruption of the viral thymidine kinase gene and expression of the hGM-CSF and β-galactosidase transgenes via adjusting the synthetic early-late and p7.5 promoters, respectively [14, 15]. Vaccinia virus has now entered a randomized controlled Phase III to express a granulocyte/macrophage-colony-stimulating factor (GM-CSF) [16]. GL-ONC1 is another class of oncolytic and immunotherapeutic vaccinia virus that has been developed for preclinical and clinical studies [17, 18]. Recently, GL-ONC1, which is administrated intravenously with chemo radiotherapy, met efficacy requirements in a Phase I clinical trial for treatment of advanced non-metastatic head and neck cancer [13]. Although oncolytic viruses are a promising gene therapy strategy for cancer therapy, several limitations are associated with their applications. The ability to infect disseminated cancer cells over distance, as well as the limited efficiency of delivering and propagating oncolytic viruses throughout the entire tumor, are challenging. This drawback might

be overcome by the extracellular enveloped virus through escaping clearance and allowing infection of distant tumor sites [19]. The need to increase systemic antitumor immunity to affect disseminated disease that generally evolves over time is another issue [20]. The potential effect of microbiota in host responsiveness to oncolytic viruses or other vaccinia viruses remains unknown. Microbiota is typically assumed to be significant in the initiation, progression, and dissemination of several cancers, as well as in patient responsiveness to interventional immunotherapies, such as immune checkpoint blockade and immunogenic tumor cell death, inducing chemotherapies [19]. Also, the functions of a large number of genes encoded by the viral genome of vaccinia virus are unclear.

2.2 Herpes Simplex Virus

Herpes simplex virus (HSV) is a double-stranded DNA genome capable of delivering up to 50 kbp of transgenic DNA when used as a vector with more than 150 kb in length. HSV is classified into short and long unique segments and flanked by inverted repeated sequences [21]. Although HSV vectors are mainly able to evade inactivation through host immune response, pre-existing immunity to HSV infection is prevalent within the common population in the same way as the adenovirus [22, 23]. Similar to the adenovirus, HSV vector genomes are episomal, thus they suffer from the same challenges of transient expression faced by adenovirus [24, 25]. Due to their excellent properties, HSVs are desirable vectors for gene therapy particularly for the treatment of nervous system disorders [21, 25]. Certain studies reveal the successful use of HSV vectors for the treatment of cancerous cells and tumors of neuronal origin [26-28]. Almost 90 genes are encoded by the HSV genome, many of which are non-essential for its replication cycle, enabling the delivery of very large transgenic DNA. HSV demonstrates diverse cell types with high infectivity and an ability to persist and transduce in both dividing and non-dividing cells. The hidden HSV genome remains episomal as a closed circular molecule, while it does not integrate into cellular DNA [29-31]. This unique ability, therefore, prevents isks of insertional mutagenesis. Generally, HSV is divided into three main categories for gene therapy applications, namely defective helper-dependent vectors (known as amplicons), replication-competent attenuated vectors, and replication-incompetent recombinant vectors. The amplicon possesses low immunogenicity and cell toxicity, since it carries minimal viral sequences. It is generated by means of a plasmid vector comprising the HSV origin of DNA replication, transgene(s) of interest, and HSV cleavage-packaging sequences. The replication-competent HSV vectors are attenuated versions of HSV that have the genes required for pathogenicity but are unessential for replication [24]. The replication-incompetent vectors can be produced by deleting genes essential for the lytic cycle of HSV that evoke a shorter immune response than wild-type HSV vectors and are less toxic [25]. Various forms of replication-defective HSV vectors have been formed via deleting several combinations of the immediate-early genes. The immediate-early genes encode infected cell protein (ICP)0, ICP4, ICP22, ICP27 and ICP47. These genes (except ICP47) control the expression of late and early genes that encode the essential functions for the virion structural proteins and viral genome replication, respectively. The biggest barrier to the therapeutic use of HSV is pre-existing immunity that effectively inactivates vector particles and limits transduced cells. The presence of latently infected cells is another safety challenge that may be transduced and present a good environment for the HSV vector to recombine with the wild-type genome [32, 33]. Most of these limitations can

be efficiently addressed by removal of immediate-early genes from the HSV vector that lead to lower cytotoxic activity and host immune response to viral gene products [34]. Such features enable HSV vector genome to expresses the transgene(s) for almost 30 days *in vivo* and 21 days *in vitro* [25]. These barriers are considered a benefit for cancer therapy due to their inherent ability to target the central nervous system. Thus, a wide range of studies demonstrates the use of HSV in combination with oncolytic vectors for the treatment of melanoma, gliomas, glioblastomas, ovarian, and other solid tumors [25, 35-37].

2.3 Lentiviral Vectors

Lentivirus is a single-stranded RNA that packages two copies of positive-strand RNA comprising three genes: *env*, *gag,* and *pol*. These genes have their own functions: *env* encodes the envelope proteins that coat the virus, *gag* encodes structural proteins, and *pol* encodes the reverse transcriptase, integrase, and protease enzymes that are packaged with the RNA strands [38]. The human immunodeficiency virus (HIV) was first engineered into an integrating lentiviral vector with effective delivery to both non-dividing and mitotic cells [39]. Other lentiviruses and HIV transfer six gene encoding accessory proteins, termed *nef, rev, tat, vif, vpr*, and *vpu* [38]. The lentiviral regulatory genes (*tat* and *rev*) and accessory genes (*vif, vpr, vpu,* and *nef*), are involved in first-generation lentiviral vectors. Specifically, *tat* and *rev* are essential for viral replication; *vif, vpr, vpu*, and *nef* enable survival benefits for lentiviral replication *in vivo*, while they are not required for the *in vitro* growth of the virus [40]. The accessory genes were removed in the second-generation [24], which does not prevent the delivery of genetic component to the host cell. Further attempts caused the development of third-generation lentiviral vectors that divided many *cis* DNA elements and accessory viral proteins, resulting in the development of self-inactivating (SIN) with enhanced safety [41]. Lentiviral vectors can carry almost 9 Kbp heterologous DNA organized in one or more genes. The availability of non-human lentiviruses, and the absence of pre-existing immunity in the human population capable of transducing human cells upon suitable modification, are advantages of lentiviruses [24]. They are also able to slowly proliferate or effectively transduce non-proliferating cells. Therefore, because of these unique properties, lentiviral vector-based gene delivery has been employed in diverse clinical trials such as X-linked adrenoleukodystrophy [42], Wiskott - Aldrich syndrome [43], and metachromatic leukodystrophy [44, 45]. The risk of activating oncogenes, inactivating tumor suppressor genes, or changing many other fundamental regulatory genes (a phenomenon known as “insertional mutagenesis”) is highly dependent on the site of integration and may potentially cause cancer [46-48]. The risk of mutagenesis might be decreased by using lentiviral vectors, if it is not eliminated [49]. Thus, safety regarding the development of cancer by insertional mutagenesis remains for lentiviral vectors in gene therapy. Large-scale fabrication of lentiviral vector, particularly for clinical applications, is another hurdle. The lack of a packaging cell line (defined as fabrication of lentiviral vectors centers around the use of a cell line) with stable transfection of the core packaging plasmids increases costs of lentiviral vectors and affects the production process consistency [40]. A recent approach successfully solves this challenge by applying Cre recombinase-mediated insertion of a codon modified HIV-1 gag-pol create into a constitutively expressed locus in 293FT cells [50]. *In vivo* gene therapy-based lentiviral vectors to the eye raises several difficulties including efficiency, immunogenicity, and the need for tissue-restricted promoters. Thus, the need for in-depth studies considering several

methods for modifying lentiviral vectors with improved safety will likely be vital for *in vivo* applications.

2.4 Other Viral Vectors

In addition to the above-mentioned viral vectors-based gene therapy, there is now a wealth of pre-clinical and clinical studies with various vectors containing polio, measles, and vesicular stomatitis virus (VSV).

2.4.1 Poliovirus

Poliovirus is a member of the Picornaviridae family and is regarded as the causative factor in paralytic poliomyelitis through selective destruction of motor neurons [51, 52]. The productive poliovirus replication exists in two areas in humans, including the spinal cord motor neurons and the gastrointestinal tract (GIT), as well as its associated lymphatic structures [53, 54]. These sites for poliovirus propagation occur simultaneously with CD155 (also known as poliovirus receptor) expression [55]. Poliovirus propagation in the GIT generates unclear enteric pathology and is typically silent, leading to severe safety issues. Consequently, the potential neuropathogenicity of the poliovirus should be completely removed before clinical studies. The favourable polioviruses should be: a) non-pathogenic, b) genetically stable on intratumoral replication, c) target and affect heterogeneous tumors, d) cause effective destruction of cancer cells, e) function in natural antiviral immune activation and neutralizing antibodies, f) reverse the immune suppressive microenvironment, and g) be able to employ immune effectors in tumor [55]. Currently, poliovirus is used in Phase I clinical trials for treatment of glioblastoma as the most aggressive cancer [56].

2.4.2 Measles Virus

Measles is an enveloped negative single-strand RNA virus belonging to the Paramyxoviridae family. A measles virus genome contains six genes that encode eight proteins: fusion (F), hemagglutinin (H), large (L) protein, nucleocapsid (N), phospho- (P), matrix (M), as well as the accessory proteins V and C that are encoded by the P-cistron [57]. The F and H proteins cause viral attachment and entry into host cells. There are three cellular receptors known for the bmeasles virus: the signal lymphocyte-activation molecule (SLAM; also known as CD150), membrane cofactor protein (CD46), and Nectin4 (also known as Polio virus receptor-related 4 (PVRL4) [58]. SLAM is a transmembrane glycoprotein fundamentally expressed on the surface of activated B- and T- lymphocytes, immature thymocytes, memory lymphocytes, and dendritic cells [59]. Most of the wild-type measles virus strains enter cells through SLAM. The CD46 is ubiquitously present on most normal human cells and is only used via laboratory adapted/vaccine strains MV. However, Nectin4 is used by both the laboratory/vaccine and wild-type strain measles virus. It is generally overexpressed on the surface of adenocarcinoma cells [58]. Clinically, measles virus has been developed in Phase I/II trials against malignant mesothelioma (NCT01503177), metastatic head and neck cancer, breast cancer (NCT01846091), fallopian, ovarian, or peritoneal cancer (NCT02068794, NCT02364713, NCT00408590), and multiple myeloma (NCT00450814, NCT02192775) [60].

2.4.3 Vesicular Stomatitis Virus

Vesicular stomatitis virus (VSV) belongs to the Rhabdoviridae family, genus Vesiculovirus, and is a nonsegmented, negative-sense, single-stranded RNA virus. Upon entering the cell the viral genomic RNA is released into the cytoplasm, where the positive-sense RNA (viral mRNA) is formed through the viral RNA-dependent RNA polymerase protein (RdRp) in the viral particle. The viral RNA polymerase produces antigenomic RNA in the absence of poly A tail and cap structure to replicate its viral genome in the cytoplasm of the host cells [61]. VSV does not go through a DNA intermediate during replication, similarly to other cytoplasmic RNA viruses. The viral RNAs also do not enter the nucleus of the host cell during the viral life cycle, and the viral RNAs are produced in the cytoplasm. VSV has been suggested as a desirable candidate for antitumor therapy, since it is a safe and powerful inducer of apoptosis with diverse cancer cells susceptible to killing by VSV [62-64]. Most cancers are irresponsive to the role of interferon (IFN), while in the presence of IFN normal healthy tissues are not affected by the virus [65]. A main challenge regarding VSV-based tumor therapy is whether the virus can be tolerated by cancer patients who are immunologically compromised. Various strategies have been introduced to solve this problem, including administering IFN systemically during VSV infection or development of VSV M-protein mutant [65], fabricating a recombinant VSV expressing IFNβ [66], and creating a recombinant replicating VSV with a modified surface glycoprotein [67].

3. Non-Viral Vectors Technology

Engineering viral-like vectors for RNA therapeutics development in order to improve their delivery methods and stability *in vivo* is one the challenge in pharmaceutical industries [68-77]. Numerus studies have shown that polymeric nanoparticulate systems are an efficient method for the safe and targeted delivery of DNA/RNA. Of particular note, it has found that artificial virus vehicles present several advantages including safety, low-immunogenicity, a capacity to deliver large RNA, and large-scale production capability at low cost [78-91]. These advantages make novel technology a boon to RNA therapeutics development and a strong tool for his field in creating delivery vehicles for this new class of therapeutic intervention intended for the treatment of viral and bacterial infections. Quantum dots are one of the newest materials that currently in use for delivery of genetic materials [92-94]. There are also concern of the use of biodegradable materials for successful delivery of DNA both *in vitro* and *in vivo* [95-100]. In this regards, polymeric materials have shown great interest in the development of no-viral vectors [100-105]. Among many polymeric materials, biodegradable types are more applicable for the delivery of genetic materials, because they are timely degradable and will be adsorbed to the host body after controlled release of the DNA molecules into the cells [106-110]. Although, there are more successful progress in the use of biodegradable polymers, but more researches are still needed to overcome many of their limitations [111-117].

4. Materials Technology

Materials design and combinational technology of biomaterials development have been significantly impacted on the new area of biodegradable polymeric materials [118-121]. Biomaterials are in the core of materials development for biomedical applications from the view

point of early stage detection of various diseases to treatment of end stage-therapeutic applications [122-130]. Materials for medical applications are divided into non-degradable and bio-degradable and each of them has advantages and disadvantages. From the view point of stability, non- non-degradable materials are more stable to use for some of medical implants [130-135], while they may cause some issue concerning to toxicity. In this regards, bio-degradable materials are the best choice for *in vivo* and *in vitro* application [136-142]. Delivery of genetic materials to the cytoplasm of cells is one the biggest challenge in the treatment of various e disorder diseases [143-150]. There are many steps in gene therapy technology in order to be successful both *in vitro* and *in vivo* [150-155]. The first step is to incorporate the negatively charged DNA or RNA into the gene carriers. Therefore, the stability of the formation between the DNA/RNA and the carrier is one of the most important factors in order to protect the genetic materials during the applications [156-160]. One the easiest technology is to use positively charged biomaterials to electrostatically interact with negatively charged DNA/RNA due the presence of the phosphate groups in their chemical structure backbone and to form stable micro- or nanoparticles [161-169]. The stability of the formation of micro- or nanoparticles is important to protect the degradation of genetic materials before transfection and after transfection of the host cells [170-175]. Combinational technology of three dimensional (3D) biomaterials with gene carriers can also make stable delivery of genetic materials to the cells [176-183]. In this regard, biomaterials are the best choice to form a platform for reverse transfection where cells first are seeded on the biomaterials and next the gene carrier are added on the top of 3D biomaterials and slowly diffuses into the 3D scaffolds and transfect the seeded cells [184-192]. 3D scaffolding biomaterials that are mainly used for tissue engineering applications are considered for stable gene transfection *in vitro* and apply to implant the transfected cells into the defect area of the body such as bone for tissue regeneration. Also, these 3D scaffolding biomaterials have been widely applied in regenerative medicine technology [193-200]. One of the advantages of biomaterials is combinational technology of tissue engineering and gene therapy where the genetic materials are incorporate into the biodegradable biomaterials and the host cells are seeded on the biomaterials [201-209]. The delivery mechanisms of DNA/RNA from biodegradable biomaterials are based on combination of the degradation of the carriers and diffusion of the genetic materials into the host cells. Therefore, it is important that the degradation of the biomaterials should later after the controlled release of the DNA/RNA from the carrier [210-212]. Also, biocompatibility of the materials is important factors for various cells and tissue both in vitro and in vivo to overcome toxicity of implanted of the materials [213, 214].

Arginine based polymers as gene carriers have been widely designed as non-viral vectors gene carrier with high level of transfection efficacy [215-218]. These biodegradable and biocompatible polymers of arginine-based poly (ester amide) were synthesized with a tunable structure for such a comprehensive biopolymer and have shown great impact in DNA delivery technology.

5. RNA Technology

RNA technology is a prospective new form of medicine in which in one area of RNA-based medicine, mRNAs have been created to serve as efficient vaccines to protect from the SARS-CoV-2 virus. This marks the new generation of nucleotide-based biological drugs and vaccines. Cancer in general, as well as viral infections such as COVID-19, are serious threats to the public health. RNA

technology is a major achievement in pharmaceutical development, and various RNA drugs have already been approved by the United States Food and Drug Administration. As such, it is also a boon to the national pharmaceutical industry, which is a significant contributor to the economy. The pharmaceutical industry had revenue of about $425 billion in 2020 alone, and it accounts for almost 50 percent of the pharmaceutical industry worldwide.

The development of viral-like vectors for RNA therapeutic treatments is of great economic value.

Among RNA molecules, siRNA have been widely developed for therapeutic applications [219-221]. siRNA molecules are powerful tools in developing products for pharmaceutical, biotechnology, and academic research. Several studies have shown that biodegradable nanoparticles are capable to carry siRNA molecules with high percentage of transfection and can protect the molecules from *in vitro* or *in vivo* degradation by surrounding enzymes [219]. Biodegradable natural polysaccharides have been widely used for delivery of RNA/DNA molecules and showed high level of transfection efficacy [86-91].

6. Future Prospects

The delivery technologies of genetic materials have become very effective in treating various diseases. Viruses such as retroviruses, adenoviruses, adeno-associated virus and herpes virus used for gene therapy to date are very powerful tools for therapeutics applications. However, they have several concerns for their future applications such as: risks of virals infection, immunogenicity, toxicity, limited size of gene, one copy, expensive, long procedure, stability and regulatory issues, and limited to certain tissues and cells. In this regard, no-viral vectors have become great interests to overcome the above problems of viral vectors as they shows: no infection, low toxicity, no limited on the size of gene, cheap, easy to prepare, stable, and applicable to all tissues and cells. Their main problem is very low transfection efficiency. The future prospects of using non-viral vectors in pharmaceutical industries must focus on designing nanoparticles that acts like a virus and it would be called artificial virus having similar high transfection efficiency.

Author Contributions

The author did all the research work of this study.

Competing Interests

The author has declared that no competing interests exist.

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