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The practical application of gene vectors in cancer therapy

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Abstract

Gene delivery systems for gene therapy provide a great opportunity for treating diseases from genetic disorders, cancer, and other infections. The recent development of gene delivery system has reviewed for viral delivery systems and non-viral delivery systems. The viral delivery systems have discussed for DNA-based vectors and RNA-based vectors, and the non-viral delivery systems have summarized on the bases of physical approaches and chemical methods. In the application of gene delivery systems, viral vector systems for gene therapy and polymeric gene delivery systems have briefly reviewed.

Introduction

Gene delivery system defines as a system for gene therapy that is the process of introducing foreign genetic molecule such as DNA or RNA into host cells [1,2]. Genetic molecules reach to the nuclei of host cells to induce gene expression [3]. Gene therapy has derived to provide a patient's somatic cells with genetic information for producing specific therapeutic proteins to modulate genetic diseases. The design of a gene delivery system requires a complete understanding of the interaction between targeting cells and delivery systems.

The gene delivery systems to be investigated consist of three components: i) a plasmid-based gene expression system that controls the function of a gene within the targeting cell, ii) a gene that encodes a specific therapeutic protein, and iii) a gene delivery system that controls the delivery of the gene expression plasmid to specific location within the body [4,5]. There are many different kinds of methods for gene delivery in various types of cells and tissues [6,7]. Successful gene delivery systems require the foreign genetic molecules to remain stable within the host cells, and the gene delivery systems can either integrate into the genomes or replicate themselves independently [8].

As a tool of transgene expression, viral-based vectors had emerged in the 1980's [9]. The virus as a vaccine vector was firstly used the vaccinia virus in 1984 as a way to protect chimpanzees against Hepatitis B [9]. On the other hand, non-viral gene delivery system had firstly reported on for showing cellular phenotype change via exogeneous DNA exposures [10,11]. The development of biomaterials for gene delivery had briefly reviewed by Kim et al [5,11,12].

In the present paper, the recent developments of viral delivery systems and non-viral delivery systems have discussed on the bases of the methods and materials for gene delivery systems. The viral delivery systems have reviewed for DNA-based vectors and RNA-based vectors. The non-viral delivery systems have summarized for the physical methods and chemical methods of gene delivery systems for cancer therapy. Poly(ethylenimine)s (PEIs) conjugated bio-reducible dendrimers for cancer gene delivery are introduced to gene delivery systems. The therapeutic targeting of chitosan-PEG-folate-complexed oncolytic adenovirus for active and systemic cancer gene therapy has reviewed. The oncolytic adenovirus coated with multi-degradable bio-reducible core-cross-linked pol(ethylenimine) has applied to cancer gene therapy.

Developmental approaches

i) Viral delivery systems

Virus mediated gene delivery utilizes the ability of a virus to inject its DNA inside a host cell. It takes advantage of the virus' ability to replicate own genetic materials. Virus is an effective form of gene delivery because of the virus structure preventing degradation via lyposome of the DNA [13-15]. In cancer gene therapy, a gene opens to intend for delivery package into a replication. The deficient viral particle forms a viral vector [16,17]. Virus used for gene therapy includes adenovirus, adeno-associated virus, herpes simplex virus, and retrovirus. There are two categories of cancer gene delivery systems, i.e. germline gene delivery system and somatic gene delivery system. Although the germline gene therapy may have a great potential, the germline gene delivery systems cannot use ethically [18,19]. Human gene therapy has been limited to somatic cell alteration. A remarkable development may expect in this field near future. There are three types of somatic gene therapy such as ex vivo delivery, in situ delivery, and in vivo delivery. There are no immunologic problems in the way but only the technique uses in the cases. In addition, only a small percentage of implanted cells remain viable at present [20,21]. In situ delivery system, the administration of the genetic materials goes directly into the target tissue. As most of the current delivery systems need no effective targeting, the way is proper [22-24]. In vivo delivery system, the genetic materials directly transfer into the targeting tissue.

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DNA-based viral vectors

DNA-based viral vectors are usually longer lasting with the possibility of integrating into the genome. Adenoviridae, adeno-associated virus, poxvirus, human foamy virus (HFV), lentivirus, and herpes virus are included as DNA-based viral vectors [25]. The viruses are able to deliver only a very small piece of DNA into the cells due to mutagenesis and cytophatic effects. DNA-based viral vectors for gene delivery use viral vectors to deliver genetic materials to the host cells. Viruses are efficient for delivering genetic materials to the host cells [26]. DNA-based viral vectors include plasmids containing transgenes for gene therapy [27]. Although most of the DNA-based viral drugs are in early stages of clinical trials, the classes of compounds have been emerged in recent years to yield extremely promising candidates of cancer gene therapy for a wide range of diseases including cancer, AIDS, neurological disorders such as Parkinson's disease and Alzheimer's diseases, and cardiovascular disorders [28-30].

RNA-based viral vectors

RNA-based viral vectors have developed for the ability to transcribe directly for infectious RNA transcripts. RNA-based vector has quickly expressed in the targeted forms because of no processing required. RNA-based gene delivery is not permanent and usually transient [25]. Human foamy virus, oncoretrovial vectors, and lentiviral vectors in gene therapy are included [25]. Positive sense RNA virus genome has manipulated largely because infectious RNA could transcribe directly from cDNA version of the RNA genome. Negative strand RNA virus genome has rapidly manipulated. The sophisticated approaches provide RNA-dependent RNA polymerase complexes coupled with negative-strand RNA templates [31]. RNA-based gene therapy has carried out for HIV with lenti-viral vector-modified CD 34(+) cells in patients undergoing transplantation for AIDS-related lymphoma [32].

ii) Non-viral delivery systems

Non-viral gene delivery had firstly reported by Avery et al. in 1943. They showed cellular phenotype change via Exogenous DNA exposure [33]. The non-viral based gene delivery systems include the methods of physical and chemical deliveries [7]. Comparing with viral based vectors, non-viral delivery methods of gene delivery systems are less likely to induce an immune response.

Physical approaches

Non-viral gene delivery mediated artificially by physical method uses to introduce genetic materials through the cell membranes [25]. The physical methods of cancer gene delivery include needle injection, ballistic DNA injection, sonoporation, photoporation, magnetofection, and hydroporation [25]. Needle injection is the direct injection of genetic materials using a needle. Ballistic DNA injection is the gold coated DNA articles that force into cells. Electroporation is the electric pulse that creates pores in a cell membrane to allow entry of genetic materials. Sonoporation is the sound wave that creates pores in a cell membrane to allow entry of genetic materials. Photoporation is the Laser pulse that creates pores in a cell membrane to allow entry of genetic materials. Magnetofection is the magnetic particles that are complexed with DNA and an external magnetic field, and then they concentrate nucleic acid particles into target cells. Finally, hydroporation is the hydrodynamic capillary effect that manipulates cell permeability.

Chemical methods

Non-viral chemical methods for cancer gene delivery systems use synthetic or natural compounds to form some particles that facilitate the transfer of genes into the cells [25]. The synthetic vector has an ability to interact with RNA or DNA electrostatically and bind to compact the genetic information in the accommodation of larger genetic transfers [34]. Then, non-viral chemical vectors are able to enter cells by endocytosis. In general, there are two non-viral vectors such as liposomes and polymers [7,25]. Liposome based non-viral vectors use liposomes to facilitate gene delivery by the formation of lipoplexes. The lipoplexes form spontaneously when the negatively charged DNA contacts with positively charged liposomes [25]. The polymer-based non-viral vectors use the polymers to interact with DNA to form polyplexes [7]. The application of the engineered polymeric nanoparticle has recently made non-viral system for gene delivery approaches [15].

Application of gene delivery systems

1. Cancer gene therapy

Gene therapy utilizes cancer gene delivery systems to carry the genetic materials with the goal of treating diseases such as cancer. In order to achieve a successful gene therapy, it is necessary to develop the proper cancer gene delivery systems. Gene deliveries in therapeutic settings utilize non-immunogenic vectors capable of cell specificity that is able to deliver an adequate amount of transgene expression to cause the desired effect [35]. DNA microarrays used in a variety of gene sequencing can identify the thousands of genes simultaneously with analytical software looking at the gene expression patterns [36]. As a method for application creating new classes of vaccines, the gene delivery systems have utilized to generate hybrid biosynthetic vectors to deliver possible vaccines. The vectors overcome the traditional barriers to gene deliveries by combining E. coli with synthetic polymers to create some vectors [37]. This gene therapy gives a great opportunity for treating some diseases from genetic disorder, cancer, and other infections. The non-viral vectors have a merit in their low immunogenicity and low cost reproducibility [38]. In addition, the non-viral vector has no limitation in DNA size for packing and modification with ligands to specific cell targeting [39].

2. Viral vector systems for cancer gene therapy

The commonly used gene delivery systems in clinical trials are basis on retrovirus, poxvirus, adeno-virus (Ad), adeno-associated virus (AAV), and herpes simplex virus (HSV). Those have cumulatively used in more than 60% of all clinical trials to date [40]. The Ad vectors were widely used in a number of different preclinical applications. Even in the clinic, the vectors are considering for the applications of cancer gene therapy or vaccination for short-term gene transfer to specific cell [41]. Retrovirus vectors based on the murine leukemia oncoretrovirus (MLV) had first used in clinical trials for humans [42,43]. Retroviral vectors can stably integrate their genome to enable long-term gene expression. They might be a good candidate for use in a number of therapies, including hematopoietic gene therapy. However, those cause unfortunately tumor-genesis by the integration of MLV sequences close to oncogenenes in the clinical trials [44]. Poxvirus vector has been widely applied to the gene therapy as vector, primarily as an agent of vaccination [45]. Adeno-associated virus is a candidate for the safest viral vector systems because it bases on non-pathogenic human virus. That can only replicate in the presence of a helper virus co-infection. On the other hand, herpes simplex virus (HSV) is one of the most

useful complexes in the cycles of replication and pathogenesis. HSV has successfully developed into a viral vector system that can use in neurological therapy [46]. Novel viral vector systems for gene therapy have been recently introduced [47- 49]. Several vectors of the alphavirus genus from the togoviridae family including the sindbis-virus (SIN), semliki forest virus (SFV), venezuelan equine encephalitis (VEE) have been developed into gene expression vectors for gene therapy.

3. Polymeric gene delivery systems

Polymer-based gene delivery systems in cancer gene therapy have tested and evaluated for gene transfer to humans. One of the candidates is the plasmid DNA that is able to carry the gene into the nucleus of the desired cells safely. In order to achieve the purpose, a series of chemically different cationic polymers have currently investigated [50].

Cationic polymer based gene delivery systems

In the research of drug delivery systems, the potential benefits of synthetic gene carriers have evaluated by various investigators for biopolymers such as liposomes and chitosan derivatives [40,41]. Regarding to cationic polymers for cancer gene delivery, these polymers can mask the negative DNA charges and condense the large genes into the small molecular structures. The cationic polymer-based nucleic acid is a complexes called as polyplexes. Cationic non-viral lipid-based gene carriers, 'lipoplexes' have been currently evaluated clinically [42-46]. The molecular characteristics of some cationic polymers for gene carriers bear the proton donating amines of proper pKa. The gene complexes is a key targeting delivery for gene therapy. Most researches focus on the effect of targeting ligands that are coordinated covalently to the DNA complexes. Many cationic polymers can conjugate to the targeting ligands. Poly(L-lactide) is one of candidates which have widely utilized as a polymer for attaching the targeting ligands[47-50]. Plasmid DNA condensation by cationic polymers undergoes a compaction under the wide variety of condition. The multivalent cations or cationic polymers have usually used as the condensing agents [51,52]. Kim and coworkers investigated the tertiary structure similar to that of the non-condensed plasmid DNA complexed with low hydrophobized (stearyl)-poly(L-lactide) [53]. DNA condensation still allow for the systems of attaching hydrophilic segments such as polyethylene glycol, dextran, hyaluronic acid or hydrophobic stearyl chains [54 -57].

Poly(L-lysine)(PLL)-based gene delivery systems

Poly(L-lysine)(PLL)-based gene delivery system has been widely used as a non-viral gene carrier since the formation of polyelectrolyte complexes between DNA and PLL was confirmed [58]. In addition, the surface charged can induce the non-specific adsorption of serum protein, resulting in rapid clearance of the complexes from the blood stream [59]. The PEGylation of the cationic polymer is able to ameliorate greatly the problems of aggregation, cytotoxicity, and non-specific protein adsorption in vivo [60,61]. The interaction of antibody-antigen is one of the most specific interaction in biological systems. Monoclonal antibody against leukemia-specific JL-1 antigen had conjugated with PLL by periodate-mediated oxidation of carbohydrate moiety in the antibody domain by the reaction with PLL [62].

Polyethylenimine(PEI)-based gene delivery systems

One of the most popular cationic gene carriers is polyethylenimine (PEI) due to its superior transfection efficiency and consistency in transfection for the different types of cells. PEI consists of primary amine group (25%), secondary amine group (50%), and tertiary amine group (25%), in which the two-thirds of the amines are able to protonate in a physiological milieu [63]. PEI gives a buffering effect for a proton sponge over a wide range of pH. These phenomena might be protected the DNA degradation during the maturation of the endosome to lysosome, facilitating the intracellular tracking of DNA [64]. Investigation on the linear PEIs showed the higher transfection efficiency and lower cytotoxicity compared to branch PEIs [65-68]. The linear PEI had conjugated with a monoclonal antibody against human epidermal growth factor receptor-2(HER-2) for targeting gene transfer to cancer cells [69]. The therapeutic targeting of chitosan-PEG-folate-complexed oncolytic adeno-virus has examined for active and systemic cancer gene therapy [70]. The oncolytic adenovirus coated with multi-degradable bio-reducible core-cross-linked pol(ethylenimine) has been applied to cancer gene therapy [71]. Arginine-grafted bio-reducible pol(disulfide amine) (ABP) was incorporated into the poly(amido amine) dendrimer to overcome the limitation of the low molecular weights of ABP. Thus, the dendrimer type bio-reducible polymer was used to the efficient gene delivery [72]. The polymeric oncolytic adenovirus systems has been developed and then applied to cancer gene therapy [73]. The targeted delivery of therapeutic gene is very successful and safe for cancer gene therapy. The tumor targeting RGD conjugated bio-reducible polymer has applied to VEGF siRNA expressing plasmid delivery [74]. VEGF therapeutic gene delivery using dendrimer type bio-reducible polymer has applied to human mesenchymal stem cells [75].

Supramolecular Hydrogel for Drug-Resistant Cancer Therapy

The co-administration of chemotherapeutics as well as therapeutic gene can play a synergistic effect on the cancer therapy. The targeted and sustained core-lease of chemotherapeutics and gene by injectable supramolecular hydrogels for drug-resistant cancer therapy has been examined [76]. An injectable supramolecular hydrogel formed by α-cyclodextrin and cationic amphiphilic copolymers made of methoxy-poly(ethylene glycol)-b-poly(ε-caprolactone)-b-poly(ethylene imine) with folic acid targeted group was rationally designed to achieve the sustained delivery of chemotherapeutic paclitaxel and B-cell lymphoma-2 conversion gene.

The injectable hydrogel-based drug delivery systems for local cancer therapy has been examined [77]. Injectable supramolecular hydrogels as delivery agents of Bcl-2 conversion gene for the effective shrinkage of therapeutic resistance tumors was also tested [78]. Supramolecular cyclo-dextrin nano-carriers for chemo- and gene therapy towards the effective treatment of drug resistant cancers has been studied [79]. Targeting death receptors for drug-resistant cancer therapy such as co-delivery of pTRAIL and monensin using dual-targeting and stimuli-responsive self-assembling nanocomposites was treated [80].

Conclusion and future prospects

An important goal of gene delivery system research is to develop clinically relevant vectors that use to combat elusive diseases such as AIDS, cancer, Alzheimer, etc. Promising RNA and DNA vectors have established as employing viral delivery systems. In non-viral delivery systems, the physical and chemical methods have utilized for gene delivery systems. RNA-based viral vector systems appear more superior to common DNA-based viral vector systems. Improvement of these vector parameters has created promising gene transfer systems suitable for in vitro and in vivo treatments in near future. Next steps will go to focus on advancing RNA and DNA technologies to become standard treatments in the clinical application of cancer therapy.

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