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Recent Advances in the Development of Bio-Reducible Polymers for Efficient Cancer Gene Delivery Systems

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Abstract

Gene therapy is the unique method for the use of genetic materials such as Messenger ribonucleic acid (mRNA), plasmid deoxyribonucleic acid (pDNA), and small interfering ribonucleic acid (siRNA) into specific host-cells for the treatment of inherited disorders in any diseases. The successful way to utilize the gene therapy is to develop the efficient cancer gene delivery systems. In this paper, the successful and efficient gene delivery systems are briefly reviewed on the basis of bio-reducible polymeric systems for cancer therapy. The viral gene delivery systems such as RNA-based viral and DNA-based viral vectors are also discussed. The development of bio-reducible polymer for gene delivery system has briefly discussed for the efficient cancer gene delivery of viral vectors and non-viral vectors.

Keywords: ***Cancer gene therapy; Gene delivery systems; Bio-reducible polymer; PEI-conjugated polymer; RNA/DNA***

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Introduction

The gene delivery systems of cancer therapy are essentially necessary for gene carriers to recover genetic diseases. The gene therapy is one of the most promising therapy for any diseases such as inherited disorders, cancers, and viral infections. Some of successful and efficient gene delivery systems have been recently reported in the practical applications [1-5]. The dendrimer-type bio-reducible polymers for efficient gene delivery systems have been prepared that arginine-grafted bio-reducible poly(disulfide amine) (ABP) is incorporated into the poly(amidoamine) (PAM) dendrimer, creating a high molecular weight bio-reducible polymer to overcome the limitations of the low molecular weight [6,7]. The compact polyplexes enhance cellular uptake and are less susceptible to reducing agents, resulting in greater transfection efficiency compared to ABP alone. Based on the research results, the newly developed PAM-ABP polyplexes are promising delivery systems for clinical gene therapy [6,7]. The efficient gene therapy systems with the tumor targeted bio-reducible polymers may be a strong candidate for cancer gene therapy. In this review, the development of viral vectors and non-viral vectors has briefly discussed for the cancer gene

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therapy. The gene delivery systems for RNA-based viral vectors and DNA-based viral vectors have also discussed for the development of efficient gene delivery systems.

Development of Efficient Gene Delivery Systems

Viral gene delivery systems

RNA-based viral vectors

RNA-based gene delivery is usually transient and is not permanent. Human oncoretrovial and lentiviral vectors in efficient gene therapy are useful [8]. 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 [9]. 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 [10]. 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.

DNA-based viral vectors

The viruses can deliver only a very small piece of DNA into the cells due to mutagenesis effects. DNA-based viral vectors for efficient gene delivery can use for the viral vectors to deliver genetic materials to the host cells. Viruses are efficient for delivering genes to the host cells [11]. DNA-based viral vectors include plasmids containing transgenes for the efficient gene therapy [12]. The classes of compounds have been emerged to yield extremely promising candidates of 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 [13-15]. DNA-based viral vectors are usually longer lasting with the possibility of integrating into the genome. Adenovirus, adeno-associated virus, poxvirus, human foamy virus (HFV), lenti-virus, and herpes virus are included as DNA-based viral vectors [8].

Non-viral gene delivery systems

The development of bio-reducible polymers (PAM-ABP) had showed enhanced gene delivery efficiency with low cytotoxicity. The lack of cell- targeting ability of PAM-ABP, however, is a major obstacle to successful disease specific application. On the bases of this evidence, the tumor targeting bio-reducible polymers by coupling cyclic RGD peptides to the PAM-ABP had developed. The physiological properties, transfection efficiency and cytotoxicity had investigated. The ability of RGD peptides to mediate intracellular uptake had evaluated in cancer cells. The therapeutic efficacy was demonstrated using VEGF siRNA expressing plasmid (pshVEGF) as a therapeutic gene [16]. The targeted gene delivery of therapeutics to tumor site is critical for the safe cancer gene therapy. Therefore, the arginine grafted bio-reducible poly (cystamine-bisacrylamide-diaminohexane) (PCBA-DAH) polymers (ABP) had conjugated with poly (amidoamine) (PAM). PAM-ABP (PA) had designed previously as an efficient gene delivery carrier. For the high achievement of efficacy in cancer therapy, the tumor targeting bio-reducible polymers had developed from PA-PEG1k-RGD, by conjugating cyclic RGDfC (RGD) peptides, which bind αvβ3/5integrins, to the PAM-ABP using polyethylene glycol (PEG, 1 kDa) [17]. For the confirmation of therapeutic effect, the VEGF siRNA expressing plasmid had tested and constructed. Then, the plasmid delivered into cancer cells using PA-PEG1k-RGD. The bio-reducible polymers of PA-PEG1k-RGD showed 20-59% higher cellular uptake rate into MCF7 and PANC-1 than that of non-

targeted polymers. The experimental results have demonstrated that the tumor targeting bio-reducible polymers can use for the efficient cancer gene therapy with an anti-angiogenic therapeutic gene [16,17].

Application of Gene Delivery Systems

Cancer gene therapy

Cancer gene delivery systems are essential to carry the genetic materials with the goal of treating diseases such as cancer. In order to achieve a successful cancer gene therapy, it is necessary to develop the proper cancer gene delivery systems. Cancer gene delivery in therapeutic settings utilizes non-immunogenic vectors capable of cell specificity that is able to deliver an adequate amount of transgene expression to cause the desired effect [18]. As a method for application creating new classes of vaccines, the cancer gene delivery systems have utilized to generate hybrid biosynthetic vectors to deliver possible vaccines. The vectors overcome the traditional barriers to cancer gene delivery by combining *E. coli* with synthetic polymers to create some vectors [19]. The cancer gene therapy gives a great opportunity for treating some diseases from genetic disorder in cancer and other infections. The viral vectors and non-viral vectors have a merit in their low immunogenicity and low cost reproducibility [20].

Viral vector systems for cancer therapy

The cancer gene delivery systems in clinical trials are basis on retrovirus, poxvirus, adeno-virus (Ad), adeno-associated virus (AAV), and herpes simplex virus (HSV) [21]. These have cumulatively used in more than 50% of all clinical trials. The Ad vectors had widely used in a number of different clinical applications. Retrovirus vectors based on the murine leukemia onco-retrovirus (MLV) had first used in clinical trials for humans [22,23]. Retroviral vectors can stably integrate their genome to enable long-term gene expression. However, those cause unfortunately tumor-genesis by the integration of MLV sequences close to oncogenenes in the clinical trials [24]. Poxvirus vector has been widely applied to the gene therapy as vector, primarily as an agent of vaccination [25]. Adeno-associated virus is a candidate for safe viral vector systems because it has based on non-pathogenic human virus. That can only replicate in the presence of a helper virus co-infection. HSV has successfully developed into a viral vector system that can use in neurological therapy [26]. Novel viral vector systems for cancer gene therapy have been recently introduced [27-29]. Several vectors of the alphavirus genus have been developed into gene expression vectors for cancer gene therapy including the Sindbis-virus (SIN), Semliki forest virus (SFV), Venezuelan equine encephalitis (VEE).

Non-viral vector systems for cancer therapy

Non-viral vector systems based on polymers for cancer gene therapy had tested and evaluated for gene transfer to humans. One of the candidate is the plasmid DNA that is able to carry the gene into the nucleus of the desired cells safely. For the achievement of the purpose, the series of chemically different cationic polymers have been currently investigated [30].

Cationic polymer based gene delivery systems

Regarding to cationic polymers for cancer gene therapy, the synthetic polymers can mask the negative DNA charges and condense the large genes into the small molecular structures. The potential benefits of synthetic polymeric gene carriers have evaluated by various investigators for biopolymers such as liposomes and chitosan derivatives [31,32]. The cationic polymer-based nucleic acids have called as polyplexes. Cationic non-viral lipid-based gene carriers such as lipoplexes have been clinically evaluated [33-37]. Many cationic polymers can conjugate to the targeting ligands. Poly (L-lactide) is a candidate that has widely utilized as a polymer for attaching the targeting ligands [30,38-40]. The multivalent cationic polymers have usually

used as the condensing molecular agents [41,42]. The tertiary structure similar to that of the non-condensed plasmid DNA complexed with low hydrophobilized (stearyl)-poly (L-lactide) for gene delivery systems was investigated [43].

Polyethylenimine (PEI)-based gene delivery systems

The most popular cationic gene carriers are macromolecules such as polyethylenimine (PEI) for cancer gene delivery systems [44]. That might be 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 [45]. Investigation on the linear PEIs showed the higher transfection efficiency and lower cytotoxicity compared to branch PEIs [46-48]. The linear PEI has conjugated with a monoclonal antibody against human epidermal growth factor receptor-2(HER-2) for targeting gene transfer to cancer cells [49].

Chitosan-conjugated cancer gene delivery systems

The therapeutic targeting of chitosan-PEG-folate-complexed oncolytic adenovirus has examined for active and systemic cancer gene therapy [50]. The oncolytic adenovirus coated with multi-degradable bio-reducible core cross-linked poly (ethylenimine) has been applied to cancer gene therapy [51]. Arginine-grafted bio-reducible poly (disulfide amine) (ABP) was incorporated into the poly (amido amine) dendrimer to overcome the limitation of the low molecular weights of ABP. The dendrimer type bio-reducible polymer was used to the efficient cancer gene delivery [52]. The polymeric oncolytic adenovirus systems has been developed and then applied to cancer gene therapy [53]. The tumor targeting RGD conjugated bio-reducible polymer has applied to VEGF siRNA expressing plasmid delivery [54]. VEGF therapeutic gene delivery using dendrimer type bio-reducible polymer had applied to human mesenchymal stem cells [55].

Supramolecular drug delivery for cancer therapy

The targeting controlled core-release of chemotherapeutics and gene by injectable supramolecular hydrogels for drug-resistant cancer therapy have been examined [56]. 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 was rationally designed to achieve the sustained delivery of chemotherapeutic paclitaxel and B-cell lymphoma-2 conversion gene. Injectable supramolecular hydrogels as delivery agents of Bcl-2 conversion gene for the effective shrinkage of therapeutic resistance tumors was also treated [57]. Supramolecular cyclo-dextrin nano-carriers for chemo- and gene therapy towards the effective treatment of drug resistant cancer had been studied [58]. Targeting death receptors for drug-resistant cancer therapy such as delivery of pTRAIL and stimuli-responsive self-assembling nanocomposites had been treated [59]. The injectable hydrogel-based drug delivery systems for local cancer therapy had also examined and tested [60].

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

Since the formation of polyelectrolyte complexes between DNA and poly (L-lysine) (PLL) had confirmed, poly (L-lysine)-based gene delivery systems were widely used as a non-viral gene carrier [61] The PEGylation of the cationic polymer is able to ameliorate greatly problems of aggregation, cytotoxicity and non-specific protein adsorption *in vivo* [62,63]. The interaction of antibody-antigen is one of the most specific sites in the immunogenicity of biological systems. Monoclonal antibody against leukemia-specific JL-1 antigen are conjugated with PLL by periodate-mediated oxidation of carbohydrate moiety in the antibody domain by the reaction with poly (L-lysine)-based gene delivery systems [64].

Conclusion and Future Prospects

The syntheses and evaluation of bio-reducible polymers for efficient gene delivery systems have been made over the past decade in our laboratory. Up to date, the poly (ethylenimine) (PEI)-conjugated bio-reducible polymers exhibit one of good candidates for the application of cancer gene delivery systems. To increase the transfection efficiency and to decrease the weight ratio when the polyplexes formed with pDNA or RNA, the bio-reducible of PEI (1.8kDa) has been designed with other hydrophilic polymers such as poly (CBA-DAH), PEO, and PAM-ABP. On the other hand, the VEGF gene silencing by PCDP/pshVEGF polyplexes inhibits the cell growth and proliferation rates. The bio-reducible polymers with the PEI contain a plentiful of nitrogen atoms including primary, secondary, and tertiary amine groups that are able to increase the binding affinity with mRNA, siRNA, and pDNA.

It has been concluded that the PEI (1.8 kDa)-bio-reducible polymers are one of the good candidates for the efficient cancer gene delivery systems. The improvement of the vectors has to do for the promising cancer gene delivery systems suitable in vitro and *in vivo* treatments in near future. Next step will go to focus on advancing DNA and RNA techniques to make the standard treatments in the cancer clinical therapy.

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