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Review

Polyester-based nanoparticles for nucleic acid delivery

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ABSTRACT

Gene therapy is promising for the treatment of inherited diseases and complex diseases such as chronic infections and cancer. The advancement in science and technology has extended the scope of gene therapy from gene transfer to the delivery of a variety of nucleic acids such as mRNA, antisense oligonucleotides (ASOs), siRNA and miRNA. Nanoparticle delivery systems can efficiently protect the nucleic acids from enzymatic degradation and immune recognition, facilitate intracellular transportation and assist the nucleic acid in escaping from renal and hepatic clearance, thus achieve sustained delivery to the target tissue. Aliphatic polyesters such as PLA, PLGA, PCL and PHB have entered clinic for decades for making implantable medical devices such as surgical meshes, sutures, screws, tissue repair patches and filling agents; and have been actively investigated for drug and gene delivery due to the excellent degradability and biocompatibility. Cationic polyester nanospheres, micelles and dendrimers which can efficiently condense and deliver nucleic acids have been synthesized via methods such as physical mixing, chemical conjugation and copolymerization of polyesters and cationic molecules.

1. Introduction

Gene therapy is promising for the treatment of inherited diseases and complex diseases such as chronic infections and cancer; especially in the situations when the standard treatment failed to save the terminal or severely disabling conditions [1]. Gene therapy fascinates the scientific and clinical community by its potential in eradicating diseases from their genetic roots and providing personalized medicine; however, it also faces much concerns and skepticism due to the safety and ethical issues. The advancement of science and technology has extended the scope of gene therapy from the transfection of plasmids to the delivery of a variety of nucleic acids such as mRNA, antisense oligonucleotides (ASO), short interfering RNA (siRNA), microRNA (miRNA) and DNAzymes [2]. Through long-term or transient expression or suppression of the disease-associated genes, the symptoms can be cured or alleviated. Both the traditional gene therapy and the newly developed RNA therapeutics involving mRNA, ASO, siRNA or miRNA have shown safety and benefits in clinical trials; however, their long-term safety especially when viral vectors are used as delivery tools, the persistence of therapeutic effect and their ability in outperforming the existing therapeutic methods are concerns that remain to be investigated. Hence, the market expectation and investment on nucleic acid drugs are much lower than that of small molecule and protein drugs. Compared with the two major structural classes of FDA-approved drugs (i.e. small molecules and proteins), nucleic acids suffer from more pharmacokinetic (PK) disadvantages such as sensitivity to enzymatic degradation, fast clearance, immunogenicity, and inability to enter cells [3]. Viral vectors have high transfection efficiency, however, in vivo gene therapy using viral vectors could elicit an acute immune response, resulting in inactivation of these particles by pre-existing virus-specific antibodies; or, the transfected cells that contain the viral components could be eliminated by the immune cells in a delayed immune response, leading to transient gene expression and potential damage to the target organ [4, 5]. In addition, the risk of insertional mutagenesis is another major concern of viral vectors, which varies largely among individual patients and makes the long-term safety of gene therapy unpredictable [1]. The development of non-viral vectors for the delivery of nucleic acids is an active research field and provides impetus for the translation of gene therapy from bench to bedside.

Generally speaking, non-viral delivery systems can be nucleic acid conjugates or nanoparticle formulations. Nucleic acid conjugates which are the conjugation of nucleic acids with molecules such as targeting ligands, hydrophobic moites and endosomolytic agents, significantly altered the PK of short strand RNA agents such as ASOs, siRNAs and miRNAs and have addressed a number of critical issues in delivery such as stability, immunogenicity, cellular entry, and endosomal escape [6]. However, for large and highly negatively charged plasmid DNA and self-replicating mRNA, nanoparticles are more efficient in dealing with

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the systemic delivery problems than nucleic acid conjugates which have much less influence on the overall physicochemical properties of these macromolecules. In addition, nanoparticles are useful tools for the delivery of components of CRISPR–Cas genome editing machinery (e.g. single guide RNA (sgRNA)) into human to translate this major breakthrough from research to clinic. Nanoparticle delivery systems can efficiently protect the nucleic acid from enzymatic degradation and immune recognition; facilitate intracellular transportation by endocytosis; and more importantly, could assist the nucleic acid in escaping from renal and hepatic clearance, and thus achieve sustained delivery to the target tissue. Compared to nucleic acid conjugates, nanoparticles could better protect the payload from enzymatic degradation. Musacchio et al. have shown that phosphothioethanol conjugated siRNA (siRNA-PE) prolonged the degradation time from 0.5 h to 6 h, while micelles formed with this siRNA conjugates showed no sign of degradation after 24 h [7]. In addition, due to the nanometer size and adjustable surface properties, nanoparticles could better evade renal and hepatic clearance. Wolfrum et al. demonstrated that siRNA-cholesterol conjugates (siRNA-Chol) improved the pharmacological properties of siRNA by binding to the nanosized lipoprotein particles in the blood stream; and the lipoprotein bound siRNA-Chol was 8- to 15-times more effective than the equal amount of unbound siRNA-Chol [8]. Similarly, the replacement of the phosphodiester backbone of ASOs by phosphorothioate resulted in a dramatic improvement in PK profile, owning to the fact that phosphorothioate avidly bind serum proteins such as albumin [6]. Hence, the delivery of nucleic acids using nanoparticles is an effective strategy in solving the delivery issues of nucleic acid therapeutics.

The nanoparticle delivery systems can be made of lipid, polymer, inorganic materials (e.g. gold, calcium phosphate), proteins, nucleic acids, and their combinations. Currently, the most clinically advanced nucleic acid delivery system is the lipid-based nanoparticles (LNP), which can be in the form of liposome or solid lipid nanoparticles. Among them, the stable nucleic acid-lipid particle (SNALP) formulation of siRNA targeting liver transthyretin amyloidosis (TTR) (Alnylam Therapeutics) has entered phase III clinical trial. However, the application of SNALP is largely restricted to liver diseases due to the inherent preference for liver accumulation. This is a commonly observed phenomenon for LNPs because of their size (usually 100–200 nm) and hydrophobicity [9]. Moreover, LNPs also suffer from drawbacks such as complex toxicity profile due to their multicomponent nature; instability in physiological environment; and low encapsulation efficiency [10]. Gold nanoparticles (Au NPs) have entered clinic trails as CT contrast agents and drug delivery systems due to the bio-inertness; and have also been widely investigated for the delivery of nucleic acids. Nevertheless, Au NPs are non-degradable and can accumulate in liver or kidney for months [11]. Although Au NPs with sizes smaller than 6 nm can be eliminated efficiently by renal clearance, the catalytic activity and hence the in vivo toxicity increases at the same time. Polymeric nanocarrier is another major class of nucleic acid delivery system. Back to the 1960s, cationic diethylaminoethyl (DEAE) dextran was shown to strongly enhance the poliovirus RNA transfection [12]. Since then, cationic polymers such as poly-L-lysine (PLL), polyamidoamine (PAMAM), polyethylenimine (PEI) have been widely investigated for the delivery of nucleic acids. Transferrin-PLL was shown to efficiently condense plasmids and bring them into receptor overexpressed cells; however, the transfection efficiency is moderate due to the endosomal entrapment. Attachment of adenovirus to transferrin-PLL significantly increased endosomal escape, resulting in the first polymer-based human gene therapy clinical trial [13]. Instead of relying on the virus for endosomal escape, polymers such as PEI and PAMAM have the “proton sponge effect” and can escape from the lysosome by osmotic pressure and membrane destabilization. The high transfection efficiency of PEI and PAMAM making them the most widely investigated nucleic acid carrier materials nowadays; nevertheless, they have not been approved in clinic due to the non-degradability and molecular weight related toxicity. Reducing the molecular weight alleviates the toxicity, but at a cost of reducing the transfection efficiency. In order to improve the clinical relevance, biodegradable polymers such as polysaccharides, polyesters, polypeptides etc., are increasingly investigated as nucleic acid delivery vehicles.

2. Polyesters

Biodegradable polyesters such as polylactic acid (PLA), poly(lactic-*co*-glycolic acid) (PLGA), poly(ε-carprolactone) (PCL), poly-β-hydroxybutyric acid (PHB) etc., have entered clinic for decades as the materials for making medical devices such as surgical meshes, sutures, screws, pins, stents, tissue repair patches and filling agents [14]. Besides, they are actively investigated as materials for constructing drug/gene delivery systems and tissue engineering scaffolds [15–18]. PEG-PLA micelle formulation of paclitaxel (Genexol-PM) has been approved in South Korea for the treatment of breast, lung and ovarian cancer; and is now in phase II clinical trials in the U. S. (clinicaltrals.gov) [19]. In addition, aptamer conjugated PEG-PLA (BIND-014) micelles have been evaluated in clinical trials as delivery vehicle for anti-cancer drug [20]. Currently, polyester is the only type of synthetic polymer that has entered clinical trials for the application of drug delivery, and one important reason is its excellent safety profile. PLA, PLGA, PCL and PHB are not only degradable in physiological environment but also bioresorbable; meaning that their degradation product can be eliminated through natural pathways by simple filtration or metabolism [21]. This process reflects the total elimination of the initial foreign material and their degradation by-product, guaranteeing that there will be no residue side effect in the long run. The degradation is mainly through hydrolysis of the ester bonds. In addition, different from bulk materials, nanoparticles and low molecular weight polymer fragments can also be taken up via phagocytosis by cells such as macrophages and giant cells and undergo intracellular degradation [22, 23]. It has been found that the degradation products of PLA and PCL could enter the citric acid cycle and be eliminated [24, 25]. The hydrolytic degradation of PHB releases β-hydroxybutyric acid (3HB), which is a natural constituent of human blood [14]. Nevertheless, direct encapsulation of nucleic acids into these polyester nanoparticles by double emulsion solvent evaporation (DESE) method usually results in low encapsulation efficiency, large particle size and slow release rate. Making the polyester nanoparticles cationic can improve the encapsulation efficiency and reduce the particle size through nucleic acid complexation and condensation, and at the same time accelerate polymer degradation by basic catalyzed hydrolysis [22]. Cationic polyester nanoparticles have been synthesized by modifying polyesters with cationic molecules (incl. cationic polymers) through physical mixing, chemical modification and copolymerization. In the following sections, recent advances in polyester-based nucleic acid delivery systems including nanospheres, micelles and dendrimers are discussed with examples.

3. Polyester-based nucleic acid delivery systems

3.1. Nanospheres

3.1.1. Physical mixing

Cationic polymers (e.g. PEI, PLL, chitosan) have been absorbed on the anionic surface of PLA and PLGA nanoparticles to create cationic surfaces for absorbing the nucleic acids [3]. The layer-by-layer structure is widely applied for the co-delivery of small molecule drug and nucleic acid agents; however, it suffers from drawbacks such as premature release and unfavorable surface properties. Encapsulation of nucleic acid into polyester nanoparticles can prevent premature release and facilitate sustained and controlled gene delivery. By simply mixing PEI (Fig. 1B) (0.3 wt%) with PLGA during the w/o/w DESE procedure, Patil et al., demonstrated continuous release of 80% of encapsulated siRNA in 15 days [26]. PLL (Fig. 1C) has also been used to condense

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