Polymeric Nanoparticles for Cancer Gene Therapy

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ABSTRACT

Developments in biomaterials have driven enhancements to nanoparticle stability and tissue targeting, conjugation of ligands to the surface of polymeric nanoparticles enable binding to specific tumor cells, and the design of transcriptional elements has enabled selective DNA/RNA expression specific to the tumor cells. Collectively, these characteristics have enhanced the performance of polymeric nanoparticles as targeted non-viral gene delivery vectors for cancer treatment. Since polymeric nanoparticles are biodegradable, non-toxic, and to have reduced immunogenicity and tumorigenicity compared to viral vectors, they have substantial therapeutic potential for clinical use. In this article, various natural and synthetic polymers used in designing polymeric nanoparticles for targeted cancer gene therapy are reviewed.

Introduction

In cancer gene therapy, nucleic acids (DNA/RNA) are delivered to cancer cells (a method known as transfection) to either initiate the expression of harmful proteins that are able to kill them or to inhibit the function of crucial proteins in the cells. The lack of safe and effective carrier systems is a major barrier to the successful translation of cancer gene therapy to the clinic. The DNA/RNA carriers that are presently existing are restricted by issues such as immunogenicity and a lack of selectivity, that is, they can deliver genes to both tumour and normal cells [1,2]. A promising alternative for such carrier applications is cationic polymer-based nanoparticles [3]. These nanoparticles are formed through electrostatic interactions between anionic nucleic acids and cationic polymers. The nucleic acids encapsulated within nanoparticles are safeguarded against possible degradation in the circulatory system. In addition, nanoparticles also passively accumulate in tumors, rather than in healthy tissues. This passive tumour targeting phenomenon has the ability to reduce non-specific dissemination while preserving on-target effectiveness. However, macrophages, a particular form of immune cell which is responsible for removing cellular debris and infectious agents, can easily eliminate several nanoparticle systems from circulatory system.

Therefore, vital organs with a large population of resident macrophages (such as the liver and lungs) often show a high degree of non-specific nanoparticle aggregation. As a result, non-target delivery of nucleic acids is still a major concern with cationic nanoparticles and enhancing targeting efficacy is a key problem for cancer gene therapy [4]. To overcome these issues recently various groups have developed functionalized polymers through the conjugation of targeting ligands (aptamer, peptide, lipids, small molecule and antibody/antibody fragment etc.) for delivering DNA/RNA to tumour sites effectively. Polymeric nanoparticle platforms are characterized by their unique physicochemical structures, including polymeric micelle, solid polymeric nanoparticles, polymer conjugate, polymer some, dendrimer, polyplex, and polymer-lipid hybrid system. This mini review will cover the natural and synthetic polymers used to make nanoparticles for the delivery of genes to tumor sites (Table 1).

Table 1.

Nature of the polymer	Name of the polymer	Advantages	Disadvantages
Natural	Albumin Alginate Chitosan Gelatin	Availability Less toxic Biocompatibility	Structural complexity Extraction and purification
Synthetic	Polylactide (PLA) Poly (lactide-co-glycoloide) PLGA Poly(epsilon-caprolactone) PCL Poly (malic acid) PMLA Poly acrylamide (PAM) Poly (isobutylcyanoacrylate) PIBCA Poly (isohexylecyanoacrylate) PIHCA Poly (n-butylcyanoacrylate) PBCA Poly(acrylate) and poly(methacrylate)-Eudragit Poly (vinyl alcohol) PVA Polyethylene glycol PEG Poly (lactide)-poly (ethyleneglycol) PLA-PEG Poly(epsilon-caprolactone) poly (ethyleneglycol) PCL-PEG Poly(lactidecoglycolide)poly(ethyleneglycol) PLGA-PEG Tween 20 and Tween 80 Dextran	Biocompatibility Long duration of release	Toxic Non-degradable Synthesis

Polymers used in the Preparation of Nanoparticles

Various materials are available for the preparation of nanoparticles such as polymers, lipids and inorganic metals (gold, silver, silicon, platinum etc.). Nature has also designed nanosized particles, specifically viruses for tissue-specific targeting and imaging agents in vivo [5]. Due to their stability, gene loading capacity and tunable properties polymers have been playing a vital role as carrier in formulating a competent gene delivery system. Biodegradable and biocompatible polymers are more advantageous than other materials for this application because of the need of appropriate release of the gene as well as easy removal of the carrier after gene release [6]. The selection of polymer for preparing nanoparticles depends upon the desired size and surface characteristics of the particle and nature of the genes or active ingredients. Physicochemical properties of the polymer determine the fabrication process employed to form matrix-based nanoparticles.

Two types of polymers are widely used for preparing nanoparticles in gene delivery

a)   Natural or bio polymers-these polymers are hydrophilic in nature

b)   Synthetic polymers- these polymers are hydrophilic in nature

Popular Biodegradable Polymers for the Preparation of Nanoparticles

Albumin: Albumin is a natural transport protein that delivers vitamins, minerals and medications all around the body. This natural transport function, cellular interactions and multiple binding sites provides rationale for its use in gene delivery. Importantly albumin is constituted by a single polypeptide chain of 585 amino acids and contains a low amount of methionine and tryptophan and a large amount of glutamic acid, cysteine, lysine, aspartic acid and arginine. Another major advantage of albumin in gene delivery is therapeutic gene of interest can be easily attached by covalently or non-covalently. Albumin is biodegradable and has functional groups that can be used to bind different ligands and DNA/RNA (e.g., apoptin, p53) [7,8].

Alginate: Alginate, a naturally occurring anionic polysaccharide of α-L-guluronic acid and β-D- mannuronic acid repeating units linked by a 1→4 linkage is widely used for pharmaceutical applications. It is biodegradable, non-toxic, inexpensive, readily available, and has been found to be a mucoadhesive, biocompatible, and non-immunogenic substance. Specifically, the simple aqueous-based gel formation of sodium alginate in the presence of divalent cations such as $Ca2+$ has been used for gene delivery [9]. Alginate based nanoparticulate delivery system was developed for frontline ATDs (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol).

Chitosan: Chitosan is a modified natural cationic polysaccharide prepared by chemical deacetylation of chitin, the second most abundant natural biopolymer after cellulose that is derived from crustacean shells [10]. The primary amino groups in the polymer backbone of chitosan provide positive charge on its surface. Due to its structure and physical, chemical and biological properties like easily modifiable, nontoxicity and adhesivity chitosan has been regarded as a potential gene carrier in the gastrointestinal tract. Another important feature of using chitosan as gene carrier is its metabolic degradation in the body. In addition, chitosan also provides easy elimination process after gene administration,

generally by renal clearance; however, this applies for chitosan with suitable molecular weight. For very large molecular weight chitosan, enzyme degradation is required, and degradation depends on the molecular weight and degree of acetylation of the polymer. It can also be used as a diluent/ filler in the gene delivery systems [11]. Chitosan has many potential applications in gene delivery via the oral, nasal, transdermal, parenteral, vaginal, cervical and rectal routes [12].

Gelatin: Gelatin is a natural, biocompatible, biodegradable, bioactive, inexpensive, non-toxic and multifunctional polypeptide for use in efficient gene release. It is a polyampholyte having both cationic and anionic groups with hydrophobic groups and it can be obtained from acid/ alkaline/enzymatic hydrolysis of collagen. The gelatin molecule chain contains ∼13% lysine and arginine (makes gelatine positively charged), ∼12% glutamic and aspartic acid (makes gelatine negatively charged) and ∼11% leucine, isoleucine, methionine and valine (makes gelatine hydrophobic) amino acids and ∼64% glycine, proline and hydroxyproline amino acids. Commercially, gelatin is available as both cationic (gelatin type A, isoelectric point (pI) 7–9) or anionic (gelatin type B, pI 4.8–5) protein without the necessity of additional functionalization [13].

Poly-D,L-Lactide-co-Glycolide (PLGA) and Poly Lactic Acid (PLA)

PLGA (poly-D,L-lactide-co-glycolide) and PLA (poly lactic acid) have been extensively studied for gene delivery as stable gene carriers. These are widely used polyesters because these undergoes hydrolysis in the body and produces biologically compatible and metabolite monomers lactic acid and glycolic acid which further enter into citric acid cycle. The degradation of PLGA and PLA is an autocatalytic process in which acid degradation products generated in the interior of the carrier accelerate the degradation process. The gene release depends on the degradation rate. A wide spectrum of PLGA types with different molecular weight and PLA/ PGA weight ratio are available in the market, which determines the biodegradation and release rate. Polymers with higher molecular weight usually exhibits lower degradation rates compared to higher molecular weight polymers. The Food and Drug Administration (FDA) and European Medicine Agency (EMA) have approved the use of PLGA and PLA in humans [14]. PLGA and PLA have been used to form nanoparticles by overcoming the dissolution and bioavailability problems of poorly water-soluble drugs. Their low intrinsic toxicity, form of encapsulating matrices and well-studied degradation kinetics make these polymers useful in gene delivery systems. PLGA and PLA are the most commonly used synthetic polymers for the creation of 3D structures in the form of scaffolds in tissue engineering research [15].

Poly-ε-caprolactone (PCL): Poly-ε-Caprolactone (PCL) is a synthetic aliphatic polyester which has received great attention worldwide for use in gene delivery systems. It is biocompatible, biodegradable and hydrophobic (water insoluble) polymer suitable for gene delivery carrier due to a high permeability to many hydrophobic drugs and at the same time being free from toxicity. It can form compatible blends with other polymers. Owing to its slow biodegradation it is ideally suitable for long-term delivery extending over a period of more than one year. Several genes have been encapsulated in PCL for targeted gene delivery [16,17].

Conclusion

Polymeric nanoparticle-based cancer gene therapy is still in its early stages at the clinical trials but has a bright future. Polymeric nanoparticle-based approaches to gene therapy have lagged in transfection efficacy relative to viral vector-based gene therapies, but they have enhanced safety, lower risks of immunogenicity and tumorigenesis, improved manufacturing and quality control, enhanced targeting capabilities, and far greater nucleic acid carrying ability. With developments in transfection efficacy and tumor specificity through various targeting approaches, polymeric nanoparticle-based gene therapy has a promising future.

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