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Nonviral Gene Delivery: What We Know and What Is Next

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Xiang Gao,[1] Keun-Sik Kim,[1] and Dexi Liu[1]

[1]Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261

Abstract

Gene delivery using nonviral approaches has been extensively studied as a basic tool for intracellular gene transfer and gene therapy. In the past, the primary focus has been on application of physical, chemical, and biological principles to development of a safe and efficient method that delivers a transgene into target cells for appropriate expression. This review summarizes the current status of the most commonly used nonviral methods, with an emphasis on their mechanism of action for gene delivery, and their advantages and limitations for gene therapy applications. The technical aspects of each delivery system are also reviewed, with a focus on how to achieve optimal delivery efficiency. A brief discussion of future development and further improvement of the current systems is intended to stimulate new ideas and encourage rapid advancement in this new and promising field.

Keywords: Gene delivery, gene therapy, nonviral vectors, transfection

Introduction

The primary challenge for gene therapy is to develop a method that delivers a therapeutic gene (transgene) to selected cells where proper gene expression can be achieved. An ideal gene delivery method needs to meet 3 major criteria: (1) it should protect the transgene against degradation by nucleases in intercellular matrices, (2) it should bring the transgene across the plasma membrane and into the nucleus of target cells, and (3) it should have no detrimental effects.

Viral vectors are able to mediate gene transfer with high efficiency and the possibility of long-term gene expression, and satisfy 2 out of 3 criteria. The acute immune response, immunogenicity, and insertion mutagenesis uncovered in gene therapy clinical trials have raised serious safety concerns about some commonly used viral vectors. The limitation in the size of the transgene that recombinant viruses can carry and issues related to the production of viral vectors present additional practical challenges. Methods of nonviral gene delivery have also been explored using physical (carrier-free gene delivery) and chemical approaches (synthetic vector-based gene delivery). Physical approaches, including needle injection,[1] electroporation,[2,3] gene gun,[4,5] ultrasound,[6] and hydrodynamic delivery,[7,8] employ a physical force that permeates the cell membrane and facilitates intracellular gene transfer. The chemical approaches[9-12] use synthetic or naturally occurring compounds as carriers to deliver the transgene into cells. Although significant progress has been made in the basic science and applications of various nonviral gene delivery systems, the majority of nonviral approaches are still much less efficient than viral vectors, especially for in vivo gene delivery. In this review, we will briefly discuss the advantages and limitations of the nonviral gene delivery systems that are shown to be active for in vivo gene delivery. We will also highlight approaches toward development of improved nonviral systems for human gene therapy. We hope that our discussion here will stimulate new thoughts and efforts toward advancement of this diverse and promising new field.

Gene Transfer by Needle Injection of Naked DNA

Simple injection of plasmid DNA directly into a tissue without additional help from either a chemical agent or a physical force is able to transfect cells. Local injection of plasmid DNA into the muscle,[1] liver,[13-15] or skin,[16] or airway instillation into the lungs,[17] leads to low-level gene expression. Specific or nonspecific receptors on the cell surface that bind and internalize DNA have been implicated as a mechanism, though the details are sketchy at this point. Nevertheless, gene transfer with naked DNA is attractive to many researchers because of its simplicity and lack of toxicity. Practically, airway gene delivery and intramuscular injection of naked DNA for the treatment of acute diseases and DNA-based immunization, respectively, are 2 areas that are likely to benefit from naked DNA-mediated gene transfer, provided that further improvements are made in delivery efficiency and duration of transgene expression. A broad application of naked DNA–mediated gene transfer to gene therapy may not be conceivable because DNA, being large in size and highly hydrophilic, is efficiently kept out of the cells in a whole animal by several physical barriers. These

Corresponding Author: Dexi Liu, Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261. Tel: (412) 648-8553; Fax: (412) 383-7436; E-mail: dliu@pitt.edu

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include the blood endothelium, the interstitial matrices, the mucus lining and specialized ciliate/tight junction of epithelial cells, and the plasma membrane of all cells. In addition, DNA degradation by intra- and extracellular nuclease activities further reduces the chance that DNA entering nuclei will be intact and functional. The current strategy for improving naked DNA–based gene transfer is to include in DNA solution substances capable of enhancing the efficiency of DNA internalization by target cells. For example, transferrin has been shown to enhance transfection in vitro.[18] The addition of water-immiscible solvents,[19,20] non-ionic polymers,[21] or surfactants,[22] or the use of hypotonic solution,[23] has also been shown to elevate gene transfer across cell membranes. Also, several nuclease inhibitors have been shown to enhance naked DNA–mediated gene transfer in cultured cells,[24] muscle,[25] and lungs.[26]

Gene Transfer by Physical Methods

Physical approaches have been explored for gene transfer into cells in vitro and in vivo. Physical approaches induce transient injuries or defects on cell membranes, so that DNA can enter the cells by diffusion. Gene delivery employing mechanical (particle bombardment or gene gun), electric (electroporation), ultrasonic, hydrodynamic (hydrodynamic gene transfer), or laser-based energy has been explored in recent years.

Transfer by Gene Gun

Particle bombardment through a gene gun is an ideal method for gene transfer to skin, mucosa, or surgically exposed tissues within a confined area.[4] DNA is deposited on the surface of gold particles, which are then accelerated by pressurized gas and expelled onto cells or a tissue. The momentum allows the gold particles to penetrate a few millimeters deep into a tissue and release DNA into cells on the path. Such a simple and effective method of gene delivery is expected to have important applications as an effective tool for DNA-based immunization. Further improvements could include chemical modification of the surface of the gold particles to allow higher capacity and better consistency for DNA coating, and fine-tuning of the expelling force for precise control of DNA deposition into cells in various tissues.[27]

Gene Transfer by Electroporation

Electroporation is a versatile method that has been extensively tested in many types of tissues in vivo,[2,3] among which skin and muscles are the most extensively investigated, although the system should work in any tissues into which a pair of electrodes can be inserted. For example, Hasson et al demonstrated that electroporation substantially increased transgene expression in isolated lung in an ex vivo organ culture setting,[28] and Dean et al showed that such a strategy also worked in live animals when a pair of electrodes was placed on the chest.[29] The level of reporter gene expression obtained was 2 to 3 orders of magnitude higher than that with plasmid DNA alone. DNA as large as 100 kb has been effectively delivered into muscle cells.[30] Long-term expression over 1 year after a single electroporation treatment was seen.[31] Gene transfer by electroporation showed less variation in efficiency across species than did direct DNA injection. The amount of DNA and how well the injected plasmid DNA distributes within the treated tissue prior to electroporation appear to have an important impact on transfection efficiency. It was also reported that age of the recipient animals affects the transfection efficiency in mice.[32] Treatment of muscle with hyaluronidase prior to injection of plasmid DNA to loosen up the surrounding extracellular matrix significantly enhanced transfection, possibly because of improved distribution of plasmid DNA in the tissue.[32,33] Alternatively, plasmid DNA administration through the portal vein followed by localized electroporation on rat liver resulted in widespread transfection in hepatocytes in the treated lobe but not in the surrounding lobes.[34] This result raises the possibility that one can supply cells with plasmid DNA via blood circulation and then apply electroporation to a selected area to achieve localized gene transfer. A short time interval between DNA administration and electroporation is critical to minimize DNA degradation by extracellular nucleases.

Several major drawbacks exist for in vivo application of electroporation. First, it has a limited effective range of ~1 cm between the electrodes, which makes it difficult to transfect cells in a large area of tissues. Second, a surgical procedure is required to place the electrodes deep into the internal organs. Third, high voltage applied to tissues can result in irreversible tissue damage as a result of thermal heating.[35] Ca^{2+} influx due to disruption of cell membranes may induce tissue damage because of Ca^{2+}-mediated protease activation.[36] The possibility that the high voltage applied to cells could affect the stability of genomic DNA is an additional safety concern. However, some of these concerns may be resolvable by optimizing the design of electrodes, their spatial arrangement, the field strength, and the duration and frequency of electric pulses.

Ultrasound-Facilitated Gene Transfer

The discovery that ultrasound can facilitate gene transfer at cellular[37] and tissue levels[38] expands the methodology of gene transfer by physical methods. A 10- to 20-fold enhancement of reporter gene expression over that of naked DNA has been achieved. The transfection efficiency of this system is determined by several factors, including the frequency,

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the output strength of the ultrasound applied, the duration of ultrasound treatment,[39] and the amount of plasmid DNA used. The efficiency can be enhanced by the use of contrast agents or conditions that make membranes more fluidic.[40,41] The contrast agents are air-filled microbubbles that rapidly expand and shrink under ultrasound irritation, generating local shock waves that transiently permeate the nearby cell membranes. Unlike electroporation, which moves DNA along the electric field, ultrasound creates membrane pores and facilitates intracellular gene transfer through passive diffusion of DNA across the membrane pores.[37,42] Consequently, the size and local concentration of plasmid DNA play an important role in determining the transfection efficiency. Efforts to reduce DNA size for gene transfer by methods of standard molecular biology or through proper formulation could result in further improvement. Interestingly, significant enhancement has been reported in cell culture and in vivo when complexes of DNA and cationic lipids have been used.[42,43] Since ultrasound can penetrate soft tissue and be applied to a specific area, it could become an ideal method for noninvasive gene transfer into cells of the internal organs. Evidence supporting this possibility has been presented: in one study, plasmid DNA was coadministered with a contrast agent to blood circulation, and this was followed by ultrasound treatment of a selected tissue.[44] So far, the major problem for ultrasound-facilitated gene delivery is low gene delivery efficiency.

Hydrodynamic Gene Delivery

Hydrodynamic gene delivery is a simple method that introduces naked plasmid DNA into cells in highly perfused internal organs (eg, the liver) with an impressive efficiency.[7,8] The gene delivery efficiency is determined by the anatomic structure of the organ, the injection volume, and the speed of injection. In a mouse model, the optimal condition involves 1.6 to 1.8 mL of DNA solution in saline for a 20 g mouse (8%-9% of the body weight) and an injection time of ~5 seconds via the tail vein. Mechanistically, the rapid tail vein injection of a large volume of DNA solution causes a transient overflow of injected solution at the inferior vena cava that exceeds the cardiac output. As a result, the injection induces a flow of DNA solution in retrograde into the liver, a rapid rise of intrahepatic pressure, liver expansion, and reversible disruption of the liver fenestrae.[45] Electron microscopy shows the existence of transient membrane defects in hepatocytes shortly after the hydrodynamic treatment, which could be the mechanism for plasmid DNA to enter the hepatocytes.[45] The gene transfer efficiency of this simple procedure is the highest so far achieved in vivo using nonviral approaches. Approximately 30% to 40% of the hepatocytes are transfected by a single hydrodynamic injection of less than 50 µg of plasmid DNA.[7] Various substances of different molecular weight and chemical structure—including small dye molecules, proteins, oligonucleotides, small interfering RNA, and linear or circular DNA fragments as large as 175 kb—have been delivered by this method.[30,46] The nonspecific nature of hydrodynamic delivery suggests that this method can be applied to intracellular delivery of any water-soluble compounds, small colloidal particles (molecular assembly), or viral particles. Hydrodynamic delivery allows direct transfer of substances into cytoplasm without endocytosis.

Such a simple, reproducible, and highly efficient method for gene delivery has been used to express proteins of therapeutic value such as hemophilia factors,[47,48] alpha-1 antitrypsin,[49-51] cytokines,[52] hepatic growth factors,[53] and erythropoietin[54] in mouse and rat models. Depending on the plasmid construct and the regulatory elements driving expression of the transgene, the level of gene expression in some cases has reached or exceeded the physiological level.[49-51] The fact that a bacterial artificial chromosome that contains an entire chromosomal transcription unit and replication origin (>150 kb) can be delivered successfully to the liver using this method[30] opens up many possibilities for gene therapy applications in liver-associated genetic diseases.

The real challenge for gene transfer by the hydrodynamic method is how to translate this simple and effective procedure to one that is applicable to humans. Rat liver can be transfected similarly through tail vein injection using an injection volume equivalent to 8% to 9% of body weight (T. Suda and D. Liu, unpublished data, 2006). If the same ratio is extrapolated to humans, one would have to inject up to 7.5 L of saline at a high rate, which is obviously many times over the maximal volume that a person can tolerate. However, successful liver transfection has been achieved using balloon catheter–based and occlusion-assisted infusion to specific lobes in rabbit[55] and swine models,[56,57] indicating that with modification, hydrodynamic gene delivery can become a clinically relevant procedure.

Gene Delivery by Chemical Methods

By far the most frequently studied strategy for nonviral gene delivery is the formulation of DNA into condensed particles by using cationic lipids or cationic polymers. The DNA-containing particles are subsequently taken up by cells via endocytosis, macropinocytosis, or phagocytosis in the form of intracellular vesicles, from which a small fraction of the DNA is released into the cytoplasm and migrates into the nucleus, where transgene expression takes place.

Cationic Lipid-Mediated Gene Delivery

Since 1987, when Felgner et al first reported that a double-chain monovalent quaternary ammonium lipid, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride

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effectively binds and delivers DNA to cultured cells,[58] hundreds of new cationic lipids have been developed (for review, see Liu et al[10]). These lipids differ by the number of charges in their hydrophilic head group and by the detailed structure of their hydrophobic moiety. Although some cationic lipids alone exhibit good transfection activity, they are often formulated with a noncharged phospholipid or cholesterol as a helper lipid to form liposomes. Upon mixing with cationic liposomes, plasmid DNA is condensed into small quasi-stable particles called lipoplexes. DNA in lipoplexes is well protected from nuclease degradation. Lipoplexes are able to trigger cellular uptake and facilitate the release of DNA from the intracellular vesicles before reaching destructive lysosomal compartments.

Most of our understanding of lipid-mediated gene delivery derives from characterization work on lipoplexes prepared in low-salt solution and transfection tests on cells in the absence of interfering substances such as serum. Under these conditions, the transfection efficiency of lipoplexes is affected by (1) the chemical structure of the cationic lipid, (2) the charge ratio between the cationic lipid and the DNA, (3) the structure and proportion of the helper lipid in the complexes, (4) the size and structure of the liposomes, (5) the total amount of the lipoplexes applied, and (6) the cell type. The first 4 factors determine the structure, charge property, and transfection activity of the lipoplexes. The remaining 2 define the overall toxicity to the treated cells, and the susceptibility of the cells to a particular lipid-based transfection reagent. The chemical structure of the cationic lipid has a major impact on the transfection efficiency. In general, multivalent lipids with long and unsaturated hydrocarbon chains tend to be more efficient than monovalent cationic lipids with the same hydrophobic chains. Transfection typically requires that the cationic lipid be in slight excess over DNA such that the lipoplexes have net positive charges on the surface. Spontaneous mixing between cationic lipids and cellular lipids in the membrane of the endocytic vesicles is crucial to the endosome-releasing process.[59] Spontaneous lipid mixing in endosomes becomes more profound when a non-bilayer-forming lipid such as dioleoylphosphatidylethanolamine (DOPE) is used as the helper lipid, rather than a bilayer-forming lipid, dioleoylphosphatidylcholine.[60,61] Inclusion of DOPE is believed to increase membrane fluidity and facilitate lipid exchange and membrane fusion between lipoplexes and the endosomal membrane. A high local concentration of DOPE, which has a strong tendency to form an inverse hexagonal phase, may lead to a nonbilayer lipid structure and cause membrane perturbation and endosome destruction.[62] However, some multivalent lipids have intrinsic transfection activity, and a helper lipid does not have a major impact on overall transfection activity, indicating that multivalent cationic lipids work on a different mechanism.[63,64] Often, these cationic lipopolyamines have protonable amine groups that apparently intercept the endosome maturation by absorbing protons to slow down the acidification process inside the endosomes, preventing the endosome-lysosome transition. It has also been suggested that a local destabilization effect of some micelle-forming cationic lipids on the endosomal membrane's integrity is part of the underlying mechanism of lipid-based gene delivery.[63]

Lipoplexes form spontaneously when cationic liposomes are mixed with DNA. The process involves an initial rapid association of polycationic liposomes and polyanionic DNA through electrostatic interaction, followed by a slower lipid rearrangement process.[65] The structure of lipoplexes is influenced by multiple factors, including the charge ratio, the concentration of individual lipids and DNA, the structure of the cationic lipid and the helper lipid, the physical aggregation state of the lipids (multilamellar or unilamellar liposomes, or micelles), the salt concentration, and the method of preparation. Lipoplexes come in various forms, including fully condensed lipid/DNA complexes, partially condensed lipid/DNA complexes, DNA sandwiched between cationic lipid bilayers, lipid-coated DNA arranged in a hexagonal lattice, or partially condensed DNA surrounded by a lipid bilayer.[66,67] With the same lipid composition and charge ratio, lipoplexes that are prepared from multilamellar liposomes with a size of ~500 nm and those that are intrinsically less stable exhibit better activity in transfection.[68,69]

The simplest way to prepare lipoplexes is to mix diluted solutions of plasmid DNA and preformed liposomes. The resulting lipoplexes are generally heterogeneous in size and morphology. The heterogeneity is primarily due to the relatively large sizes of DNA and liposomes, and the multivariant nature of the interaction between the DNA and liposomes. Alternative methods involving forms of lipid assembly other than liposomes have been designed to overcome these problems. For example, direct addition of DNA solution to a dried film of cationic lipid and DOPE promotes entrapment of DNA within multilamellar liposomes, rather than sandwiching of DNA between liposomes.[70] A method of lipoplex preparation by slow dialysis has also been developed. This procedure involves DNA condensation in mixed micelles consisting of cationic lipid and non-ionic detergent, and removal of the detergent by dialysis.[70] At a concentration below the critical micelle concentration of single-chain cationic lipids, DNA collapses into unimolecular lipid-DNA nanoparticles that are much smaller (20-30 nm). Small particles are preferred for in vivo gene delivery because of their slower clearance rate in the blood and, therefore, their high probability of reaching the target cells. Conjugation to these small-sized complexes with polyethylene glycol (PEG) and targeting ligands on their surface makes it possible to construct target-specific gene carriers.[71]

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Many cationic lipids show excellent transfection activity in cell culture, but most do not perform well in the presence of serum, and only a few are active in vivo.[10] A dramatic change in size, surface charge, and lipid composition occurs when lipoplexes are exposed to the overwhelming amount of negatively charged and often amphipathic proteins and polysaccharides that are present in blood, mucus, epithelial lining fluid, or tissue matrix. Once administered in vivo, lipoplexes tend to interact with negatively charged blood components and form large aggregates that could be absorbed onto the surface of circulating red blood cells, trapped in a thick mucus layer, or embolized in microvasculatures, preventing them from reaching the intended target cells in the distal location. Some even undergo dissolution after they are introduced to the blood circulation.[72,73]

Despite these undesirable characteristics, lipoplexes have been used for in vivo gene delivery to the lungs by intravenous[74-76] and airway[77-79] administration. Transgene expression was clearly detectable but in most cases was insufficient for a meaningful therapeutic outcome. For airway gene delivery to the lungs, animal studies using lipoplexes prepared from 3β-[N-(N′,N′-dimethylaminoethane) carbamoyl]cholesterol (DC-Chol) and DOPE have shown that this procedure was mild to the host and partially effective in correcting genetic defects in a cystic fibrosis transmembrane regulator mutant model.[80] By screening a large cationic lipid library in earlier studies, the Genzyme group revealed some structure-activity relationships important to the transfection activity of cationic lipids in a mouse model.[81] Several cholesterol derivatives with polyamine groups linked to cholesterol through a carbamoyl bond exhibited significantly higher activity in the lung compared with that of naked DNA or DC-Chol/DOPE lipoplexes.[81] Most transfected cells were found in the lower airways in the alveoli region, not the intended bronchial epithelial cells.

Several inhibitory factors for lipoplex-based gene delivery have been identified for airway gene transfer.[82,83] A critical factor is that upper-airway epithelial cells are covered by a negatively charged and viscous mucus layer that often traps and neutralizes the surface charges of the lipoplexes. In patients with cystic fibrosis, the epithelial cells are further covered with a thick layer of sputum that contains genomic DNA released from dead cells and bacteria. In lower airways, the surfactant layer enriched with several phospholipids and surfactant proteins is also believed to inhibit the transfection activity of lipoplexes. In addition, well-differentiated upper airway epithelial cells are known to be less active in taking up lipoplexes than are those in the lower airways. Proper shielding of surface charges of lipoplexes to reduce nonspecific protein/mucin association, inclusion of a target ligand to enhance specific binding, and substitution of a portion of the cationic lipids with less toxic and membrane-active peptide seem to be logical and incremental steps to solving some of these problems.

In vivo gene transfer by systemic administration of lipoplexes mainly transfects endothelial cells in the pulmonary vasculature.[74] A large excess of cationic lipids was needed to mediate optimal gene transfer.[74] Although using DOPE as the helper lipid makes the formulation more efficient for airway gene delivery, it has an adverse effect on intravenous transfection. Cholesterol was found to be a better helper lipid for systemic transfection.[74] In systemic gene delivery, cholesterol seems to stabilize the lipoplex structure in blood, while formulations containing DOPE tend to fall apart more easily in the presence of blood components.[72,74] Moreover, it has been shown that one can efficiently transfect pulmonary endothelial cells by injecting free cationic liposomes and following shortly thereafter with a second injection of naked DNA solution,[84] which suggests that various forms of lipoplex structures that seem to be important for transfection of cells in tissue culture are not critical for transfection by intravenous injection. The expression of a reporter gene in transfected endothelial cells in the lung follows a quick onset, which reaches its peak level ~8 to 16 hours posttransfection, then declines rapidly. The rapid decline is not solely due to DNA degradation, as a second transfection 1 week later did not result in significant expression,[74] suggesting that it is likely that initially transfected cells become resistant to the same type of transfection. The lack of cellular response by the transfected cells to subsequent transfection suggests a negative transcription regulatory mechanism.

Toxicity related to gene transfer by lipoplexes has been observed. Acute inflammation reactions have been reported in animals treated with airway instillation or intravenous injection of lipoplexes.[74] Detailed toxicological studies on one of the Genzyme Lipid formulations, GL-67/DOPE, revealed that the cationic lipid contributes significantly to the toxicity observed.[85,86] Similar toxic effects are also noticeable in systemic gene delivery via the tail vein with other types of cationic lipids. Symptoms include acute pulmonary hypotension, induction of inflammatory cytokines, tissue infiltration of neutrophils in lungs, decrease in white cell counts, and in some cases tissue injury in liver and spleen.[87] In humans, various degrees of adverse inflammatory reactions, including flulike symptoms with fever and airway inflammation, were noted among subjects who received aerosolized GL67 liposomes alone or lipoplexes.[85] These early clinical data suggest that these lipoplex formulations are inadequate for use in humans.

Part of the inflammation response seen in treated lungs is related to the unmethylated CpG (umCpG) sequences found in the plasmid of bacterial origin. A potent immune stimulant, umCpG triggers release of proinflammatory cytokines.[88,89] Cationic lipids in lipoplexes are capable of enhancing the umCpG effect.[90] Another factor related to the severity of

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